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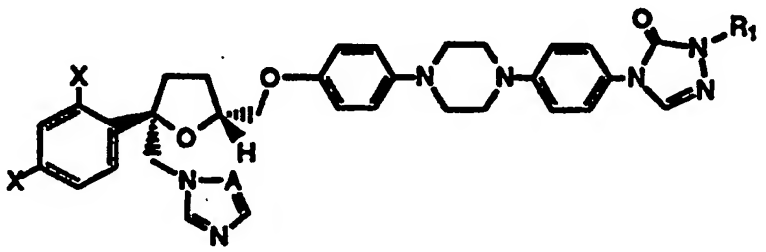
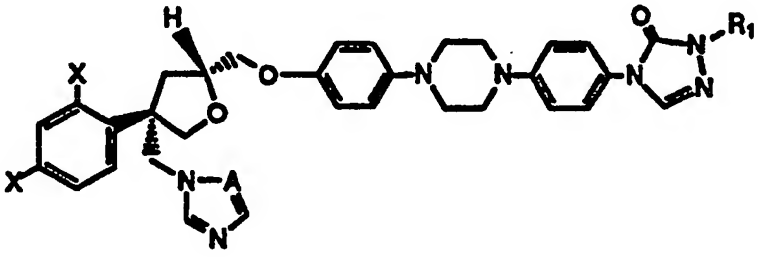
(54) Title: TETRAHYDROFURAN ANTIFUNGALS



(Ia)



(Ib)

(57) Abstract

A compound represented by a formula selected from the group consisting of (Ia) and (Ib), wherein X is independently selected from the group consisting of F and Cl; A is CH or N; R_1 is a straight or branched chain (C_3 to C_8) alkyl group substituted by one or two hydroxy moieties, an ether or ester thereof (e.g., a polyether ester, a heterocyclic ester, an amino acid ester or phosphate ester thereof) or a pharmaceutically acceptable salt thereof and pharmaceutical compositions thereof useful for treating and/or preventing fungal infections are disclosed.

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TETRAHYDROFURAN ANTIFUNGALS

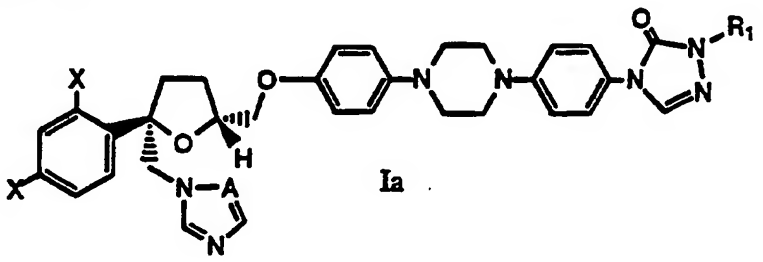
BACKGROUND OF THE INVENTION

This invention relates to tetrahydrofuran antifungals, hydroxylic derivatives, esters, ethers and salts thereof, pharmaceutical compositions containing them, and methods of treating and/or preventing antifungal infections in hosts, including warm-blooded animals, especially humans with such tetrahydrofuran antifungals.

There is a need for broad-spectrum antifungal agents having increased solubility and having favorable activity profile for treating systemic fungal infections, especially Aspergillus, Candida, Cyrptococcus and other opportunistic fungal infections.

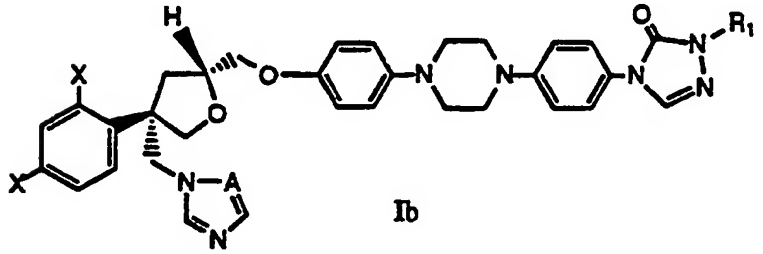
SUMMARY OF INVENTION

The present invention provides compounds represented by the following formulas



Ia

and



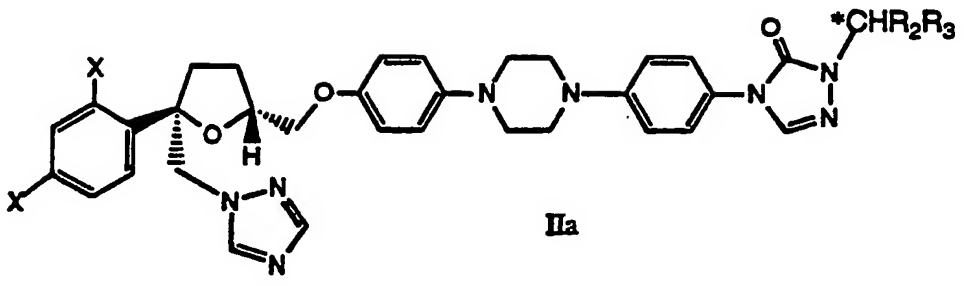
Ib

wherein X is independently selected from the group consisting of F, Cl Br, and CF_3;

A is N or CH;

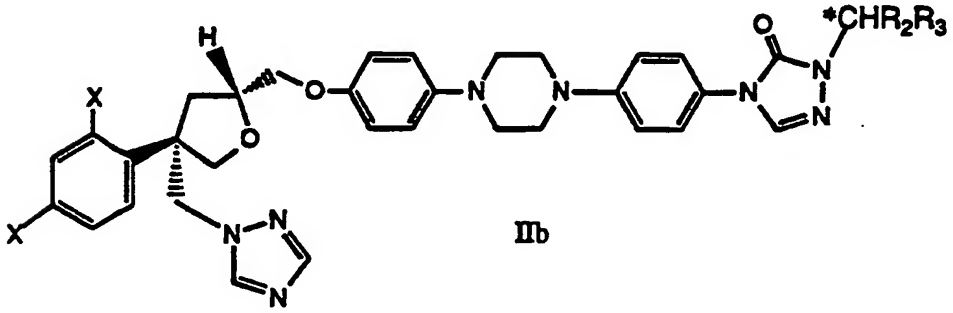
R_1 is a straight or branched chain (C_3 to C_8) alkyl group substituted by one or two hydroxy moieties or stereoisomers thereof or by one or two groups convertible in vivo into hydroxy moieties, or a pharmaceutically acceptable salt thereof.

In a preferred aspect of the present invention, there is provided compounds represented by formulas IIa and IIb



IIa

and

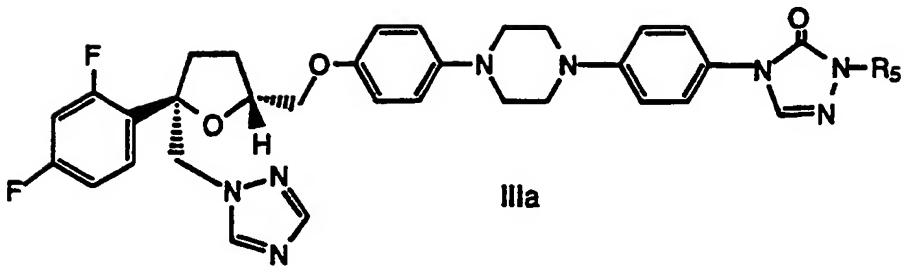


IIb

wherein X is independently selected from the group consisting of F, Cl Br, and CF_3;

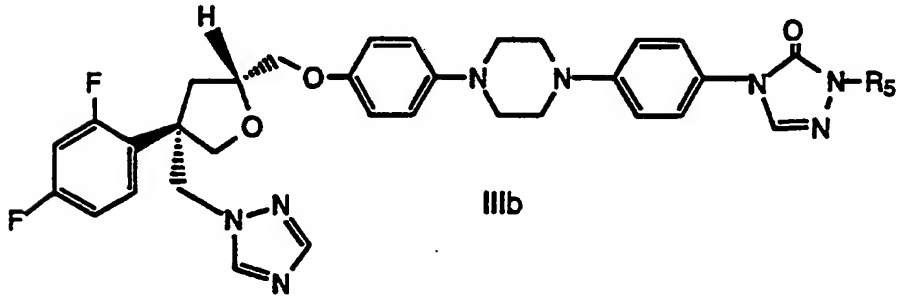
wherein R_2 is H or (C_1-C_3) alkyl and R_3 is (C_1-C_3) alkyl substituted by one hydroxy moiety or by a group convertible in vivo into a hydroxy moiety and the carbon with the asterisk (*) has the R or S absolute configuration; or a pharmaceutically acceptable salt thereof.

In another preferred aspect, the present invention provides a compound represented by formulas IIIa and IIIb



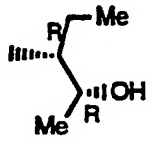
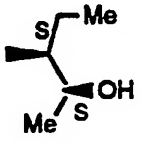
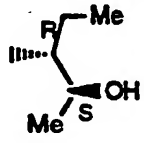
IIIa

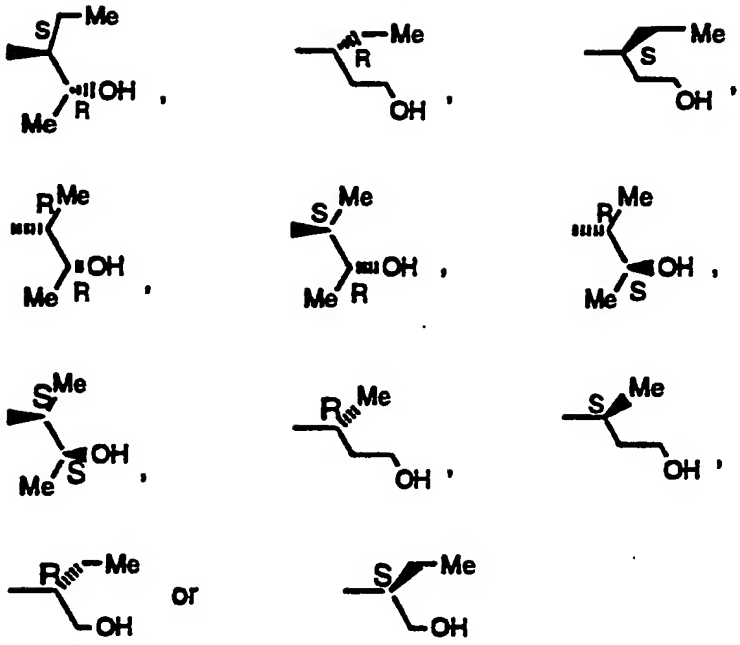
and



IIIb

wherein R_5 is

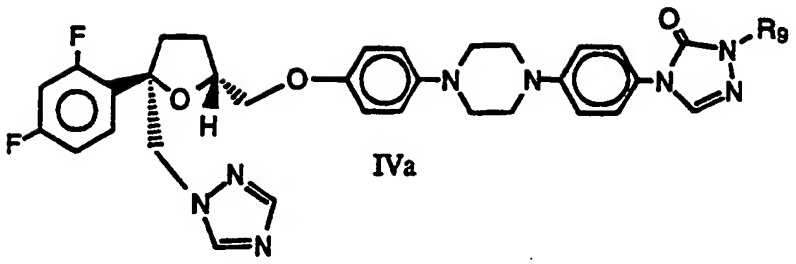






an ester, carbonate, or urethane thereof or a pharmaceutically acceptable salt thereof.

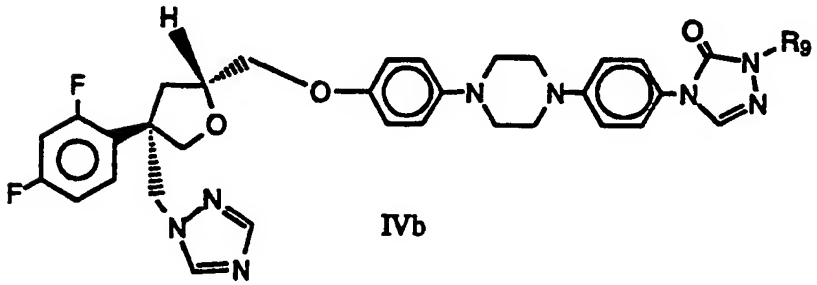
Preferably the ester or ether is a group convertible in vivo into OH e.g. a polyether ester, phosphate ester, heterocyclic esters or an amino acid ester, or a pharmaceutically acceptable salt thereof.

In another aspect of the present invention there is provided a compound represented by the formulas IVa and IV b



IVa

and

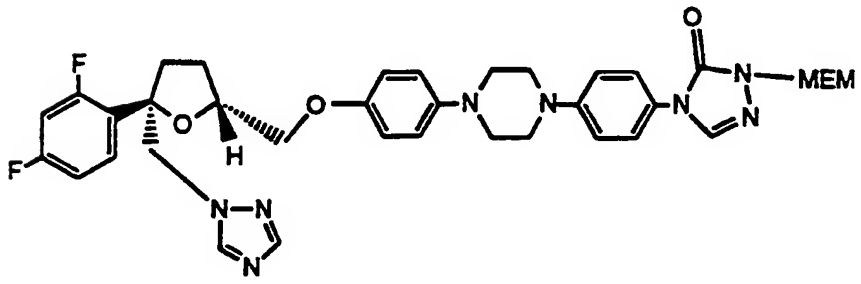


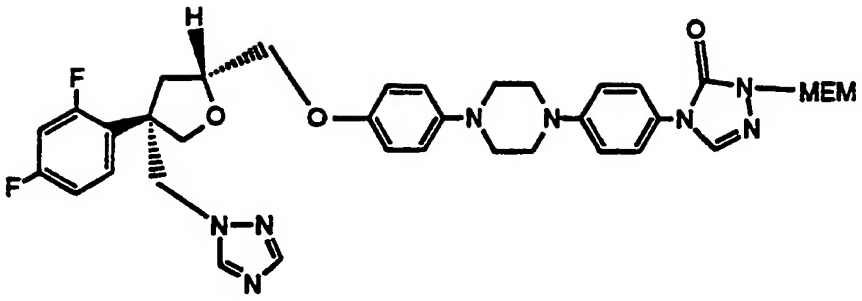
IVb

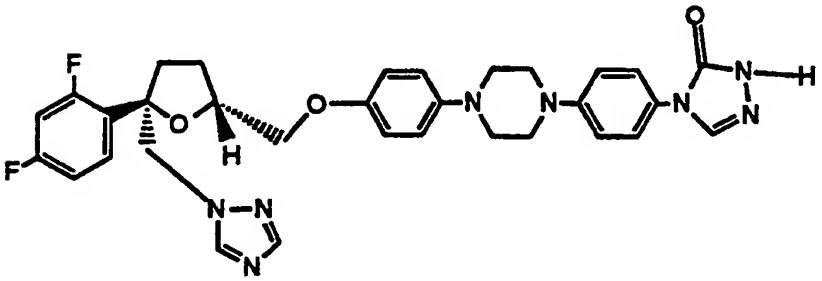
wherein R_9 = $-\overset{*}{C}H(C_2H_5)CH(R_6)CH_3$ or $-\overset{*}{C}H(CH_3)CH(R_6)CH_3$

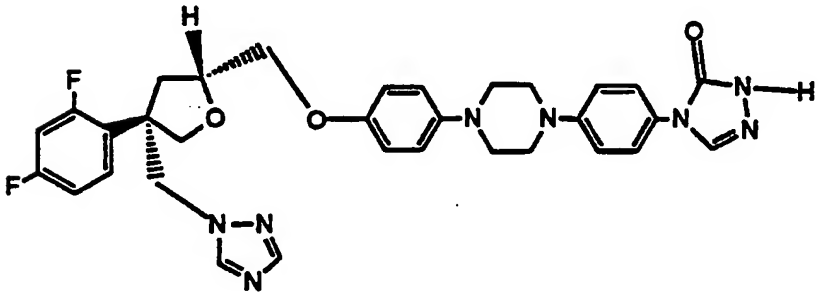
wherein R_6 is OH, or a group convertible in vivo into OH, or a pharmaceutically acceptable salt thereof.

Exemplary of the compounds of the invention are the following:

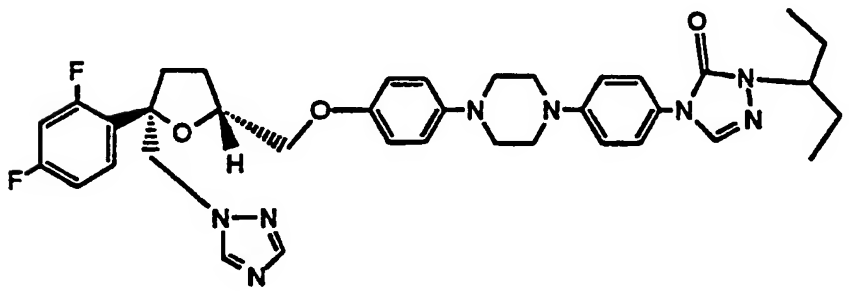



H
F
F
O
O
N
N
N
O
N
MEM
N
N
N

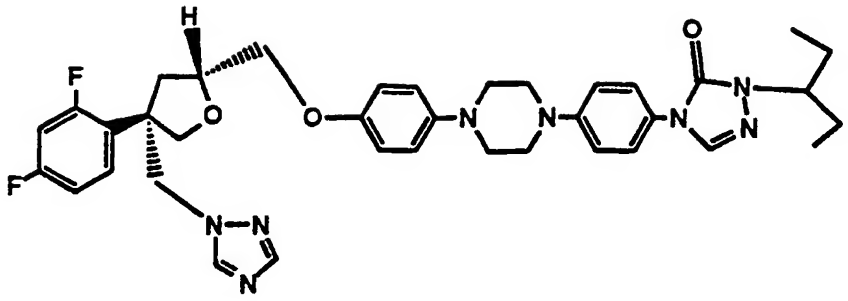

F
F
O
O
H
N
N
N
O
N
H
N
N
N

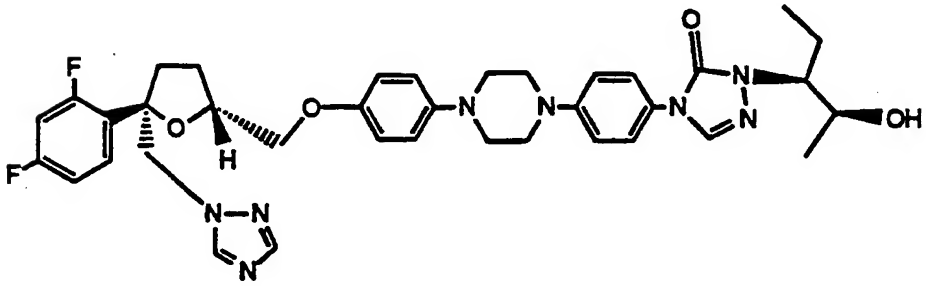

H
F
F
O
O
N
N
N
O
N
H
N
N
N

5

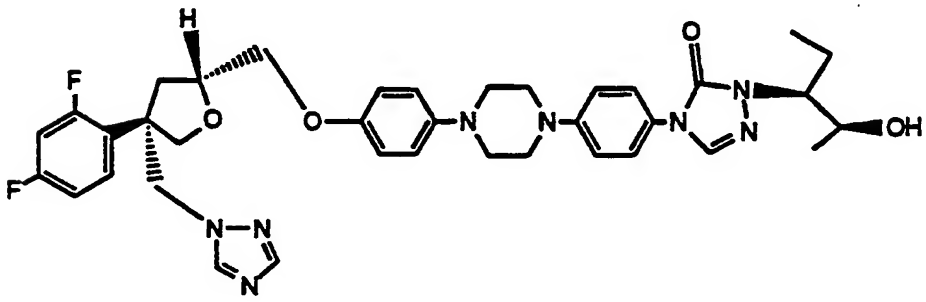

F
F
O
O
H
N
N
N
O
N
N
N
N

10



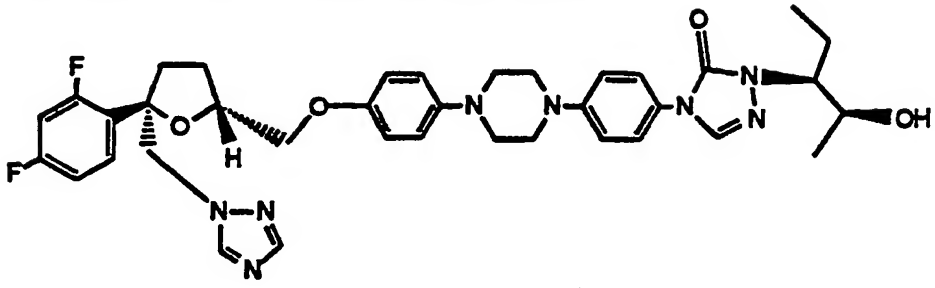


and



or a pharmaceutically acceptable salt thereof.

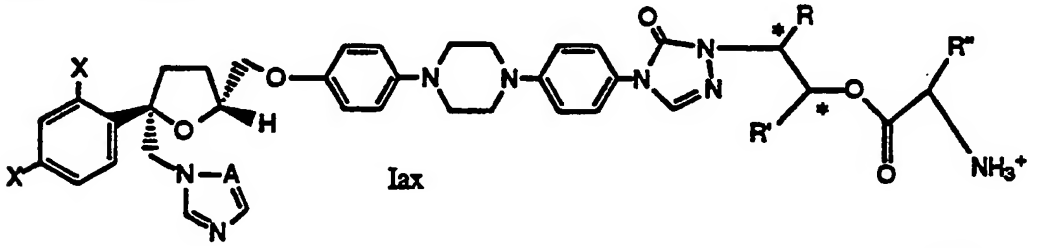
The most preferred compound of the invention is



or a pharmaceutically acceptable salt thereof; or an α-amino acid ester thereof; or a pharmaceutically acceptable salt of an α-amino acid ester thereof.

The hydroxy compound shown just above is preferred for oral use.

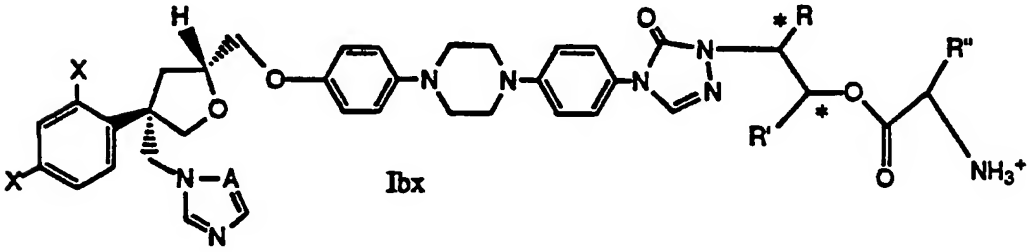
The invention further relates to amino acid esters of the type shown just below:



Iax

AN⁻

and



Ibx

AN⁻

wherein X is independently selected from the group consisting of F, Cl Br, and CF_3;

A is N or CH;

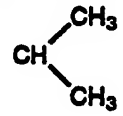
R is H, CH_3, or C_2H_5, :

R' is H, CH_3, C_2H_5 ,

AN^- is an anion such as Cl^- or $C_3H_5O_3^-$;

R" is H, CH_3, CH_2OR''', $CH(OR''')CH_3$; CH_2SR''',

, CH_2CONH_2, $CH_2CH_2CONH_2$,



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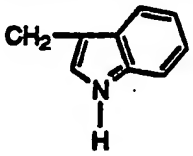
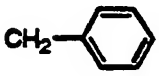


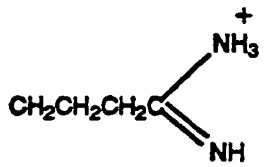
$CH(CH_3)CH_2CH_3$,



,

, $CH_2CH_2SCH_3$,

$CH_2COO^-\ M^+$, $CH_2CH_2COO^-\ M^+$, $CH_2CH_2CH_2CH_2NH_3^+\ AN^-$



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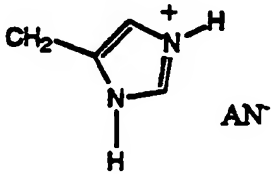


,

M^+ is a metal cation such as Na^+; and

R''' is H, phosphate ester, sulphate ester and proline ester.

An α-amino acid ester thereof which is shown just above is preferred for intravenous use.

DETAILED DESCRIPTION OF THE INVENTION

The term "(C_3-C_8) alkyl group substituted by one or two hydroxy moieties", as used herein means straight and branched chain alkyl groups of three to eight carbons including but not limited to methyl, ethyl, n- and iso-propyl, n-, sec-, iso- and tert-butyl, n-, sec -, iso-, tert and neo-pentyl n-, sec-, iso-, tert- and neo-hexyl, n-, sec-, iso-, tert- and neo-heptyl, n, sec- iso, tert-and neo-

octyl, substituted by one or two hydroxy moieties and includes R and S stereoisomers of such (C_3-C_8) alkyl groups.

The term "(C_1-C_3) alkyl substituted by one hydroxy moiety" means $-CH_2OH$, $-\overset{*}{C}H(OH)CH_3$, $-CH_2CH_2OH$, $-\overset{*}{C}H(OH)C_2H_5$, $-\overset{*}{C}H_2CH(OH)CH_3$, and $-(CH_2)_3-OH$ wherein the carbons with the asterisk(*) have the R or S absolute configuration.

The term "hydroxy-substituted C_4 or C_5 alkyl group" means $-\overset{*}{C}H(C_2H_5)\overset{*}{C}H(OH)CH_3$, $-\overset{*}{C}H(C_2H_5)CH_2CH_2OH$, $-(CH_2)_2-\overset{*}{C}H(OH)C_2H_5$, $-\overset{*}{C}H(CH_3)\overset{*}{C}H(OH)CH_3$, $-\overset{*}{C}H(CH_3)\overset{*}{C}H(OH)CH_3$ or $-\overset{*}{C}H(C_2H_5)CH_2OH$ wherein each carbon with the asterisk (*) has the R or S absolute configuration.

The term "MEM" means methoxyethoxymethyl.

The term "group convertible in vivo into OH" means a group transformable <u>in vivo</u> by e.g. hydrolysis and/or by an enzyme, e.g. an esterase into a hydroxyl group. Such groups include polyether esters, phosphate esters, sulfate esters, heterocyclic esters, alkanoate esters, alkenoate esters, carbonate esters, amino acid esters, carbamate esters, and acid esters. Preferred groups convertible <u>in vivo</u> into a hydroxyl group are the polyether esters, phosphate esters and amino acid esters.

The term "ether" as it relates to protective groups in the syntheses given herein, means (C_1-C_6) alkoxy or aryl (C_1-C_6) alkoxy which are conveniently made by the well known Williamson Synthesis of ethers. Typically suitable ether groups include methoxy and benzoxy.

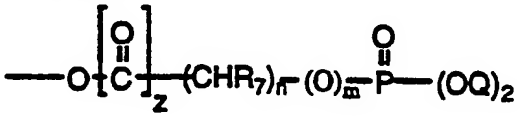
The term "esters" means (a) polyether esters (b) phosphate esters (c) heterocyclic esters (d) alkanoate and alkenoate esters (e) amino-acid esters (f) carboxylic acid esters (g) carbonic and carbamic acid esters and (h) sulfate esters.

The term "polyether esters" as used herein means those polyether esters represented by the formula $-O-\overset{O}{\overset{\|}{C}}-(CHR_7)_s-(OCHR_7CHR_7)_t-OR_8$ wherein

R_7 is a (C_1-C_6) straight or branched chain alkyl. Where more than one R_7 appear in a molecule, each R_7 may be the same or different from the others. "s" is an integer from 1 to 6, preferably s = 1 to 3 and more preferably s = 1; t is an integer from 1 to 200;

R_8 is R_7 or $-(CHR_7)_s-CO_2R_7$; preferably R_8 is CH_3 or C_2H_5 or $-CH_2CO_2H$ or $-CH_2CO_2CH_3$. Typically suitable polyether esters include $-COCH_2O(CH_2CH_2O)_1CH_3$; $-COCH_2O(CH_2CH_2O)_2CH_3$, and $-COCH_2O(CH_2CH_2O)_3CH_3$.

The term "phosphate esters" as used herein means those phosphate acids esters represented by the formula



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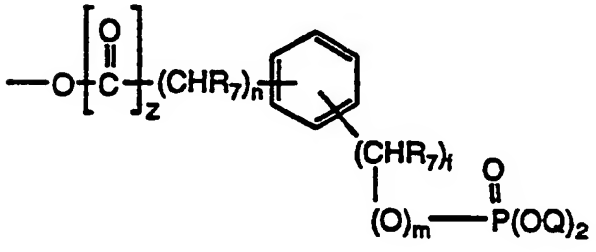
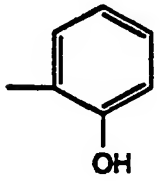
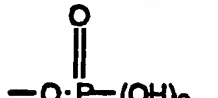
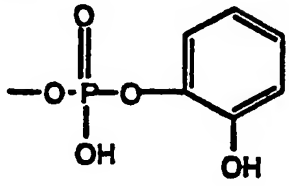
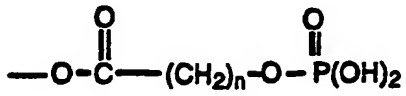


, wherein z is 0 or 1; R_7 is as defined herein above and preferably is H, and where more than one R_7 appears in a molecule, each R_7 may be the same or different from the others; n and f are independently an integer from 0 to 6, m is 0 or 1 and Q is H, CH_2Ar or

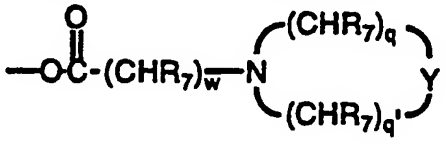


and wherein Ar is phenyl, phenyl substituted by halo, especially chloro and fluoro, or by nitro, cyano and trihalomethyl especially trifluoromethyl.

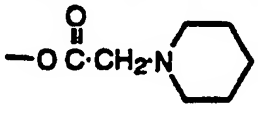
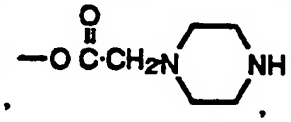
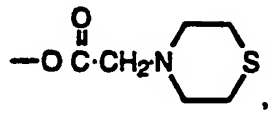
Typically suitable phosphate acids and esters include  ,

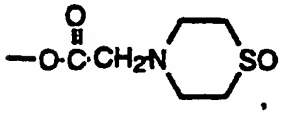
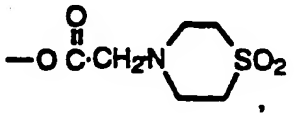
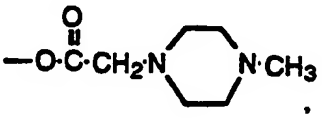
 ,  ,  ,

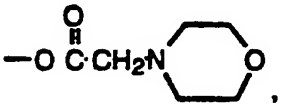
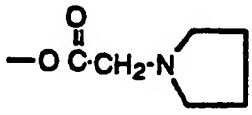
wherein m= n = 1 to 4; or  and pharmaceutically acceptable salts thereof.

The term "heterocyclic ester" as used herein means heterocyclic esters represented by the formula  wherein R_7 is as defined herein above, w is an integer of from 1 to 5 preferably w is 1 to 3; q and q' are independently 1 to 4, and q + q' are preferably equal to 2, 3, 4, or 5, and Y is CHR_7, -O-, NH, NR_7, S, SO or SO_2

Typically suitable heterocyclic esters include

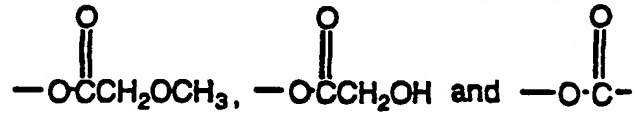
 ,  ,  ,

 ,  ,  ,

 and  .

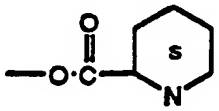
The term "alkanoate and alkenoate esters" as used herein means straight or branched chain alkanoate or alkenoate groups optionally substituted by a hydroxy or ether moiety or mixtures of such alkanoates or alkenoates.

Preferred alkanoate esters include acetate to decanoate, especially acetate to butanoate. Preferred hydroxy substituted alkanoate ester include C_1

to C_8 alkanoate substituted one hydroxy moiety or one C_1-C_6 alkoxy group, especially  .

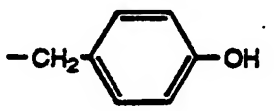
Preferred alkenoate esters are the C_{10}-C_{20} alkenoates and include C_{14} to C_{18} alkenoates, such as cis-7-hexadecenoate.

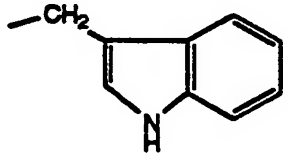
The term "amino acid ester" as used herein includes α-aminoalkanoyl-oxy, natural i.e., (L)-α -amino acid ester groups, e.g. the ester of glycine, peptide esters thereof, unnatural α-amino acid ester groups such as O-CO-CH(NH_2)(CH_2)$_3$ CO_2H, OCOCH(NH_2)(CH)$_2NH_2$,OCOCH(NH_2)(CH)$_3NH_2$



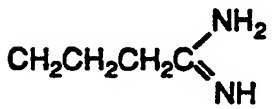
and

α -amino alkanoates represented by the formula -OCOCH ($NR_{20}R_{21}$)R_{22} wherein R_{20} and R_{21} are independently hydrogen or (C_1-C_8) straight or branched chain alkyl groups or R_{20} and R_{21} together with N form a 4, 5 or 6 membered ring optionally substituted with NR_{21}, -O- or -S- and R_{22} is H, CH_3, CH_2OH, $CH(OH)CH_3$, CH_2SH,





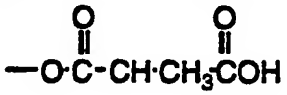
CH_2 $CONH_2$, -$(CH_2)_2CONH_2$, $CH(CH_3)_2$, $CH(CH_3)_2$, $CH(CH_3)C_2H_5$, $(CH_2)_2SCH_3$, CH_2,CO_2H, $(CH_2)_2CO_2H$, $(CH_2)_4NH_2$, -$CH_2C_6H_5$,



and pharmaceutically acceptable acid addition salts thereof, or (C_1-C_8) straight and branched chain alkyl groups optionally substituted by hydroxyl or $NR_{20}R_{21}$. Preferred amino acid acids are the natural α amino acid groups, dipeptides and α -amino alkanoates wherein R_{20} and R_{21}

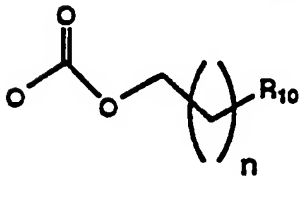
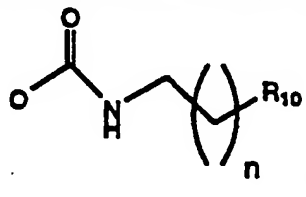
are each CH_3. The most preferred amino acid esters are those derived from alanine, phenylanine, glycine, leucine, isoleucine and valine.

The term "carboxylic acid ester" as used herein means those acid esters represented by the formula  wherein each R_7 is as defined herein above, and where more than one R_7 appears in a molecule, each R_7 may be the same or different from the others, and k is an integer of from 1 to 8. Typically suitable acid esters include oxalic, malonic, succinic, glutaric and adipic acids as well as branched chain diacids such as



Preferred salts are HCl and lactic acid.

The term "carbonic and carbamic acid esters" means

 and  respectively,

wherein n is 1, 2 or 3;

R_{10} is OH, NHR or a salt thereof; and

R is H, CH_3 or C_2H_5; .

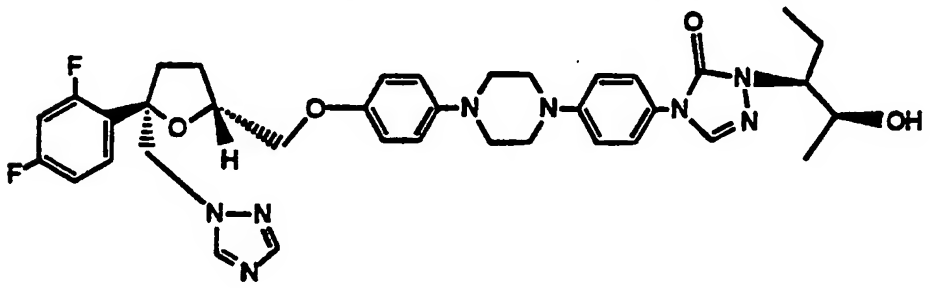
The term "LG" means a leaving group, and unless otherwise noted may be Cl, Br, I, OSO_2CH_3, $OSO_2C_6H_5$, $OSO_2(C_6H_4)CH_3$, $OSO_2(C_6H_4)Cl$, $OSO_2(C_6H_4)Br$, $OSO_2(C_6H_4)NO_2$, $OSO_2(CF_2)_pF$ where p is 1 to 4.

The term "Hal" means halogens, and unless otherwise noted may be Cl Br and I.

The term "PG" means a protecting group, and unless otherwise noted may be CH_2Ph (benzyl), CH_2OCH_3 (MOM), CH_2OCH_2Ph (BOM), $CH_2OCH_2CH_2OCH_3$ (MEM), $CH_2OCH_2CH_2Si(CH_3)_3$ (SEM)

Compounds of the invention exhibited the following in vitro antifungal activity in EMEM against 11 strains of *C. albicans* and *tropicalis*: geometric mean MICs in the range of ≥0.01 to ≥0.10(mcg/ml).

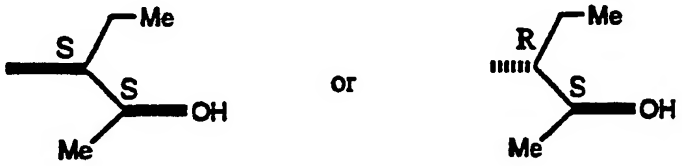
The most preferred compound of the invention,



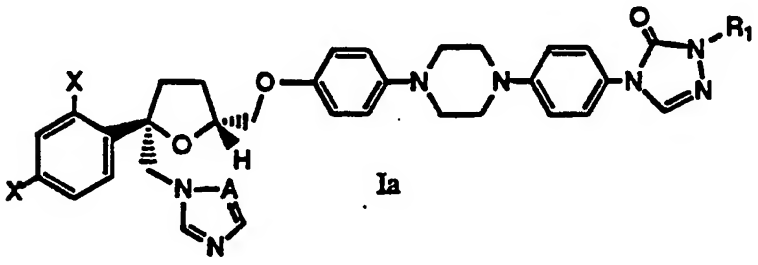
exhibited the following in vitro antifungal activity in EMEM against 11 strains of *C. albicans* and *tropicalis*: geometric mean MICs of ≥0.01 (mcg/ml).

Compounds of the invention also exhibited in vivo antifungal activity.

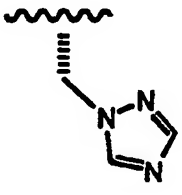
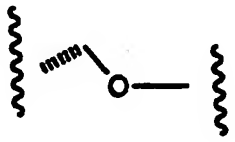
The more preferred esters listed hereinabove are water soluble and readily convertible in vivo to the corresponding alcohols *e.g.* R_5 is



Compounds of the present invention represented by formula Ia and Ib can exist in the "cis " isomeric form. With reference to formula Ia, for example,

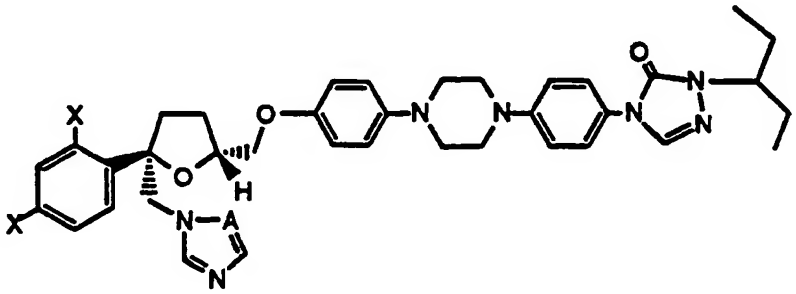


Ia

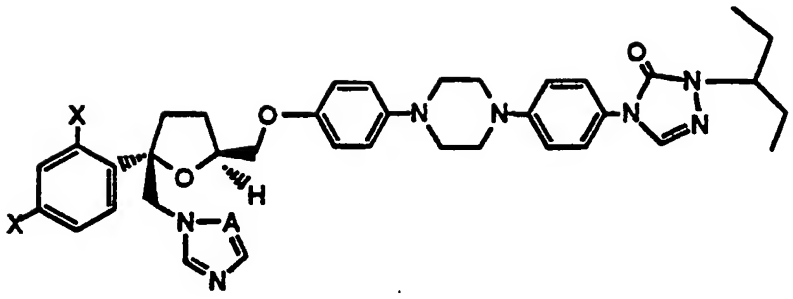
"cis" means that the  moiety and the  moiety are on the same side of the of the tetrahydrofuran ring.

The same meaning for the term "cis" attaches to formulas Ib, IIa, IIb, IIIa, IIIb, IVa and IVb and the structures of the final products of the invention.

By relative stereochemistry, it is understood that the compound just below:

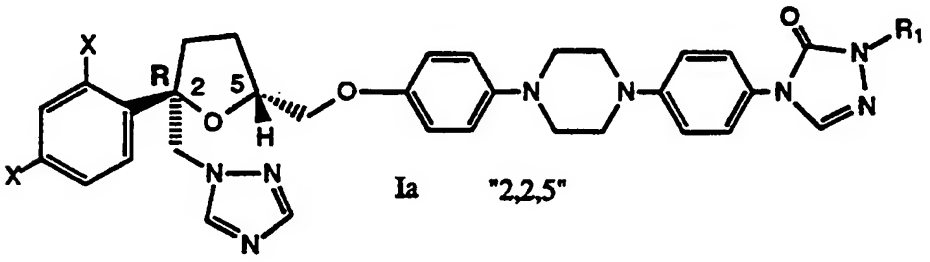


can either have the stereochemistry shown or be the enantiomer thereof, that is

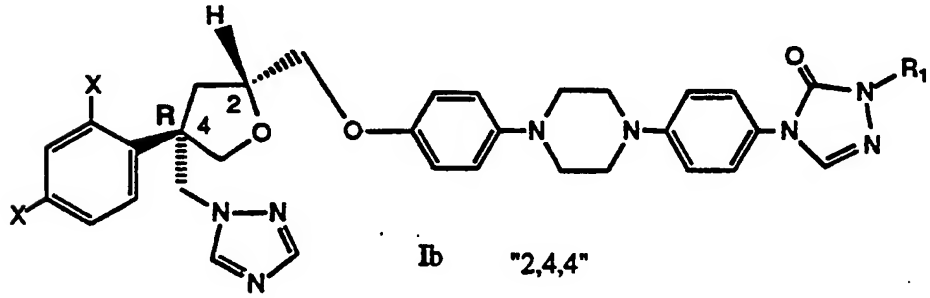


Unless otherwise indicated, structures of other compounds throughout this application which show the cis stereochemistry about the tetrahydrofuran ring are to be understood as encompassing the compound shown or the enantiomer thereof.

Certain compounds of the invention differ from other compounds of the invention with respect to the points of attachment of the various moieties to the tetrahydrofuran ring. Ring numbering for certain positions on the tetrahydrofuran ring is given for formulas Ia and Ib just below.



Ia "2,2,5"



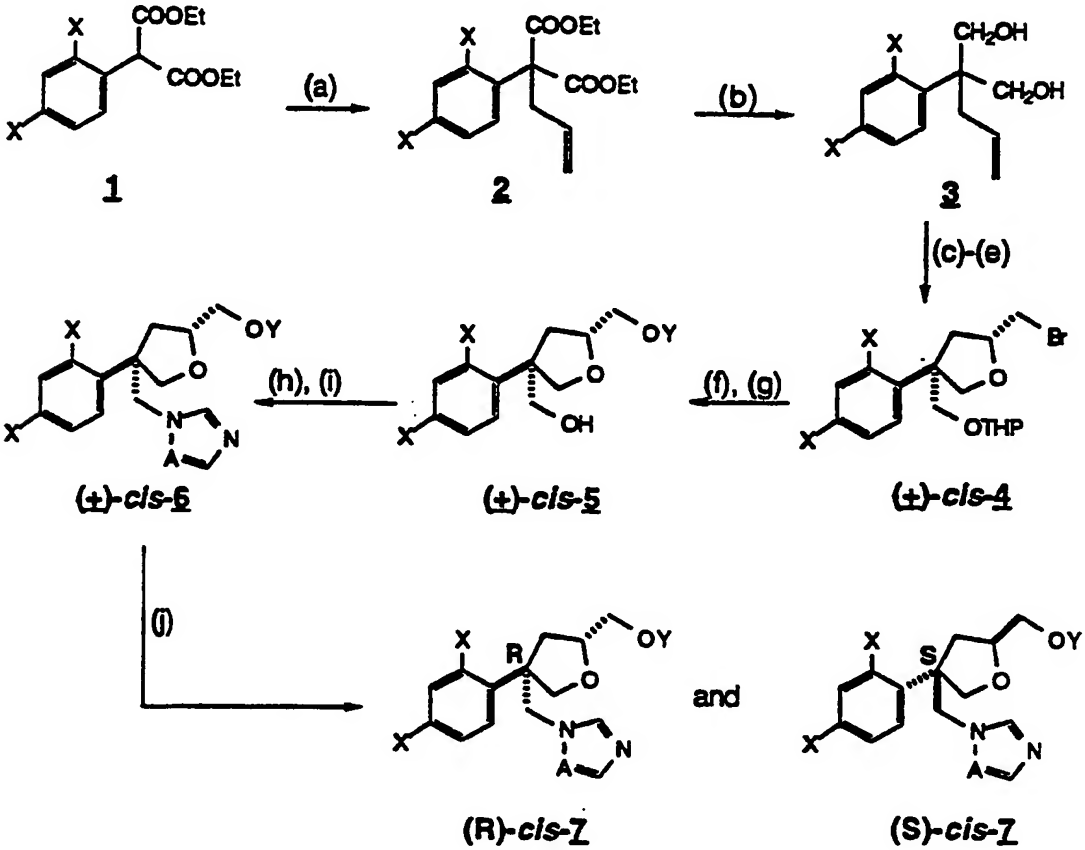
Ib "2,4,4"

From the formulas just above, it can be seen that formula Ia compounds of the invention are known as 2,2,5 compounds, that formula Ib compounds of the invention are known as 2,4,4 compounds.

GENERAL SYNTHETIC PREPARATIONS

Compounds of the invention may be prepared according to the reaction schemes shown just below. The starting materials in these reaction schemes are either known or can be prepared according to known methods.

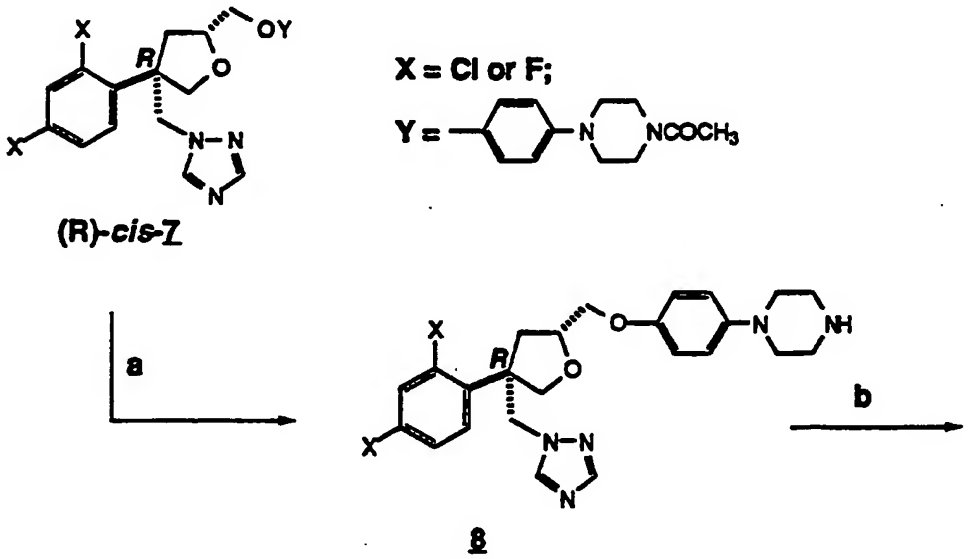
SCHEME 1: 2,4,4-Tetrahydrofuran Compounds,



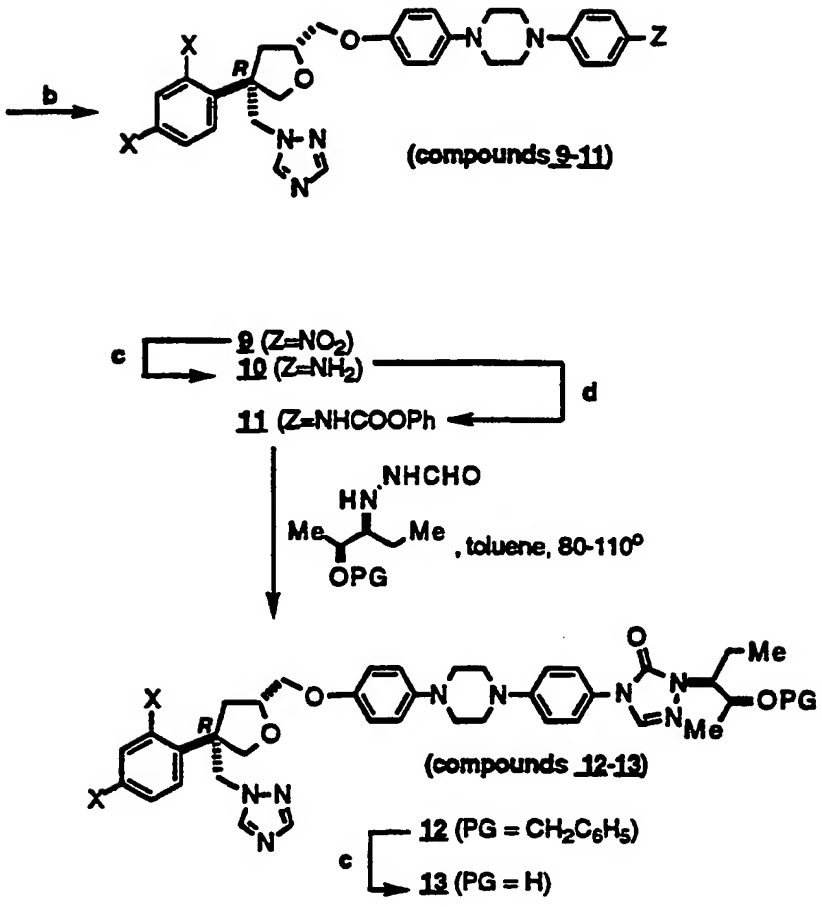
Reagents: (a) NaOEt, EtOH, allyl bromide ; (b) $LiAlH_4$, EtOEt ; (c) Br_2, CH_2Cl_2 ; (d) chromatography ; (e) Dihydropyran, H^+ ; (f) YO^- ; (g) H^+ ; (h) Mesylation ; (i) Azole anion (Z=N,CH), DMF, heat ; (j) Chiralcell chromatography, using a Daicel OD, Chiralcell column.

The reactions shown in the scheme 1 just above can be carried out in a manner analogous to that set forth in U. S. Patent 5,039,676, column 23 , line 42 through column 24, line 7. U. S. Patent 5,039,676 is hereby incorporated by reference.

SCHEME 2: 2,4,4-Tetrahydrofuran Compounds,



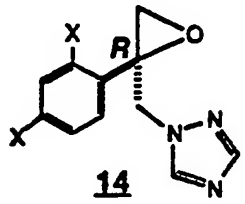
SCHEME 2: contd.



Reagents: (a) NaOH, n-BuOH; (b) *p*-Cl-$C_6H_4NO_2$, K_2CO_3, DMSO; (c) H_2, Pt-C; (d) C_6H_5OCOCl, pyridine, CH_2Cl_2.

The reactions shown in the scheme 2 just above can be carried out in a manner analogous to that set forth in scheme V, page 28 and scheme VI, page 29 of commonly assigned copending U. S. Ser. No. 08/460,752, filed June 2, 1995. U. S. Ser. No. 08/460,752, filed June 2, 1995 is hereby incorporated by reference.

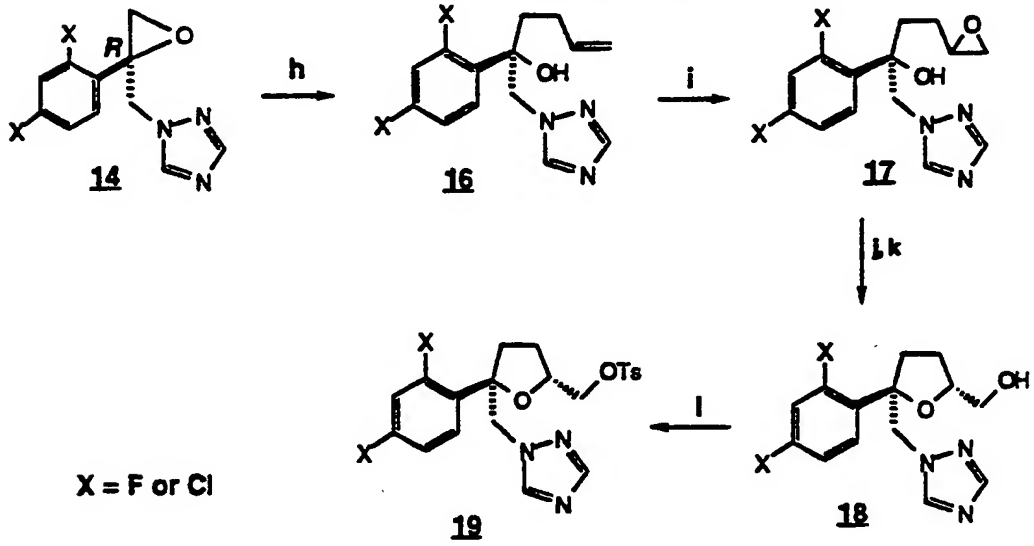
Compounds of formula 14 just below:



14

can be prepared in a manner analagous to that set forth in scheme VI, page 28 of commonly assigned copending U. S. Ser. No. 08/460,752, filed June 2, 1995.

Scheme 3

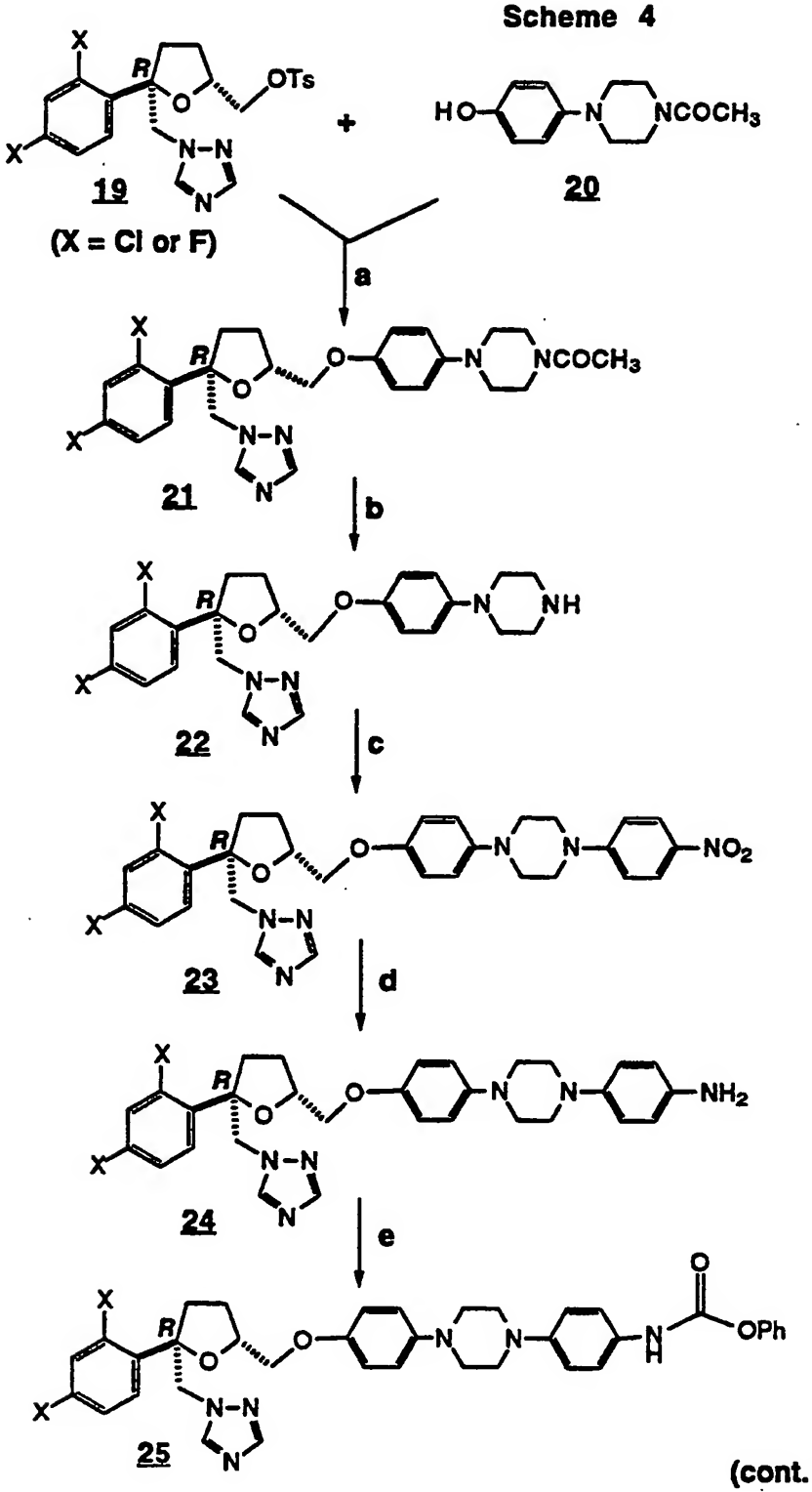


Reagents: (h) allyl magnesium bromide, CuI, THF; (i) *m*-chloroperbenzoic acid; (j) Et_3N, toluene, Δ; (k)chromatography; (l) tosyl chloride, Et_3N.

Compounds of formula 19 can be prepared as shown in scheme 3 above by treating a suitably substituted chiral epoxide, e.g 14, with an allyl magnesium halide in an appropriate solvent, e.g. THF, in the presence of a catalyst, e.g. CuI, at a suitable temperature, e.g -70°C to 0°C, to produce an hydroxylic olefin , e.g. 16. The hydroxylic olefin so produced can be treated with an appropriate oxidizing agent, e.g. *m*-chloroperbenzoic acid, in a suitable solvent, e.g. CH_2Cl_2, at 0°C to 25°C to produce an hydroxylic epoxide, e.g 17. The hydroxylic epoxide so produced can be treated with a tertiary amine base, e.g.

Et_3N, or NaH in a suitable inert solvent, e.g. toluene, at an elevated temperature, e.g. 90°C to 110°C, to produce an hydroxylic tetrahydrofuran, e.g. 18. The hydroxylic tetrahydrofuran so produced can be treated with an alkyl- or arylsulfonyl halide, e.g. toluenesulfonyl chloride, in the presence of an organic amine base, e.g. Et_3N or N,N-dimethylaminopyridine, in a suitable solvent to produce the corresponding sulfonate, e.g. 19.

Scheme 4



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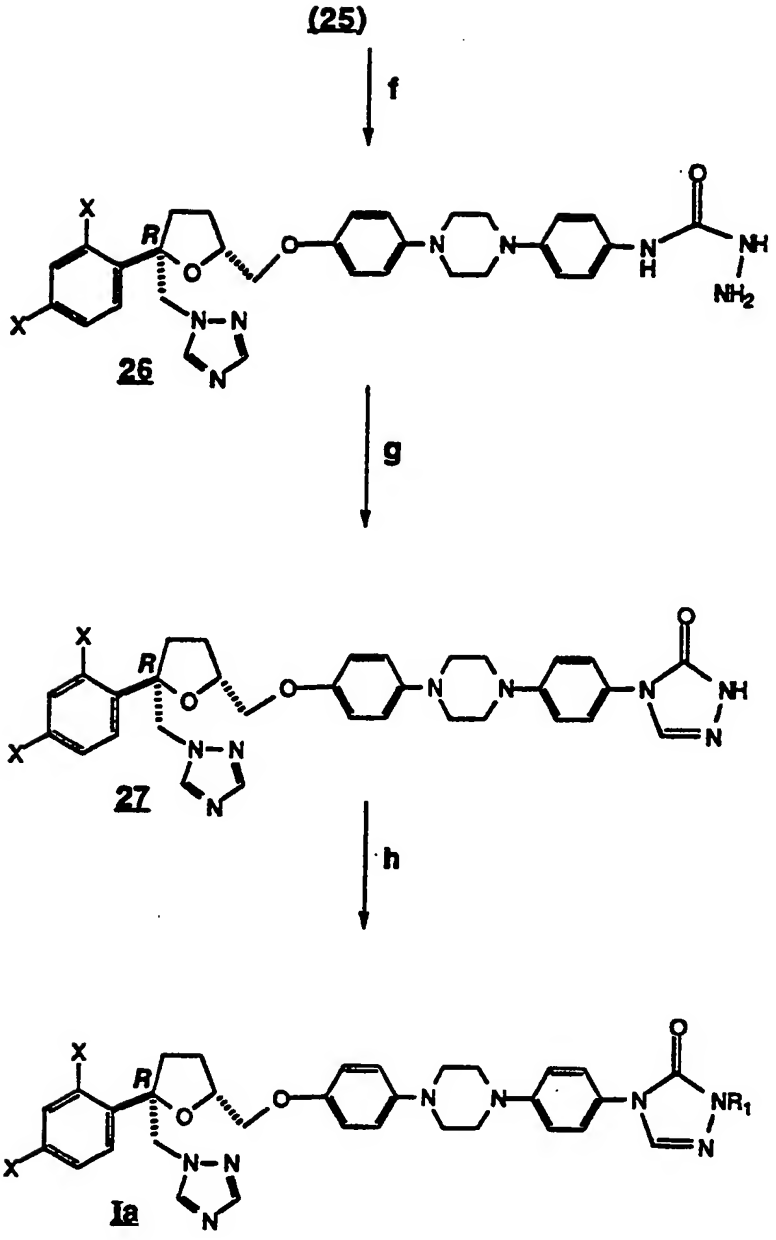
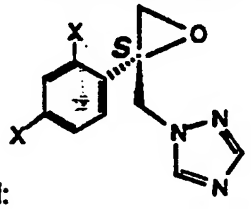


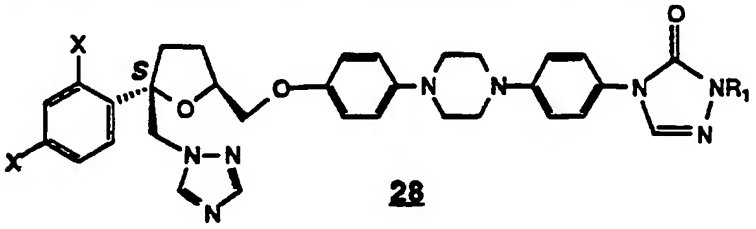
Reagents: (a) NaH, DMF; (b) NaOH, n-BuOH; (c) *p*-Cl-$C_6H_4NO_2$, K_2CO_3, DMSO; (d) H_2, Pt-C; (e) C_6H_5OCOCl, pyridine, CH_2Cl_2; (f) $NH_2NH_2.H_2O$, H_2O, dioxane; (g) formamidine acetate, DMF, 80°C; (h) according to Scheme II, pg 25 and Examples 19 and 20, of U.S. Ser. No. 08/460,752, filed June 2, 1995

The compounds of formula Ia can be prepared from compounds of formula 19 by the reactions shown in scheme 4 above carried out in a manner analogous to that set forth in scheme II, page 24, of commonly assigned copending U.S. Ser. No. 08/460,572, filed June 2, 1995.

If, in the above reaction scheme 3, the S epoxide is



used: , then the corresponding final product of different stereochemistry will be obtained from scheme 4. For example, using such a starting epoxide, the following product was obtained:



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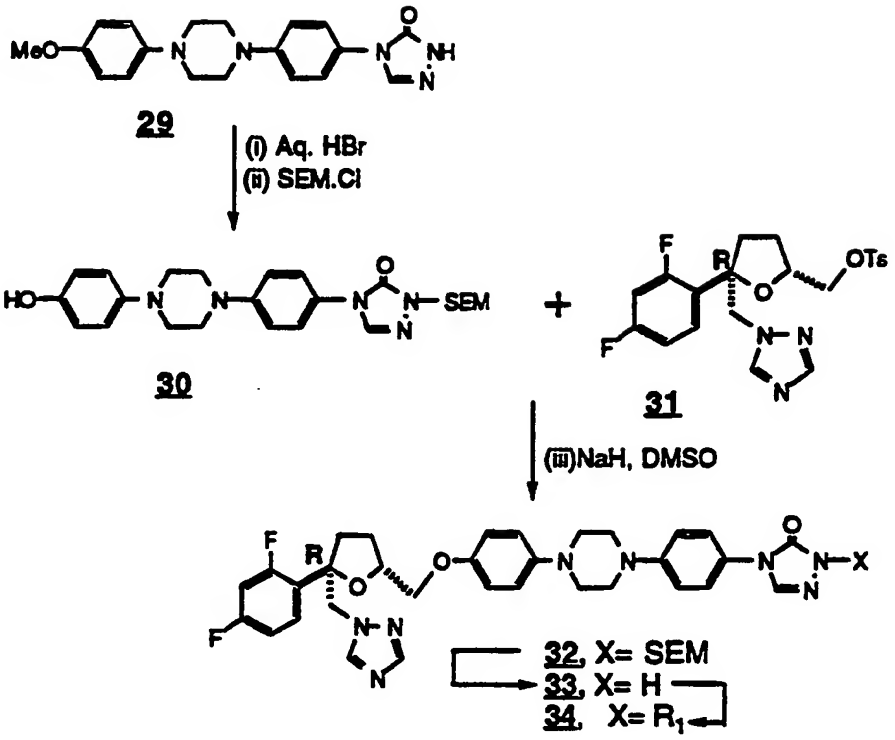
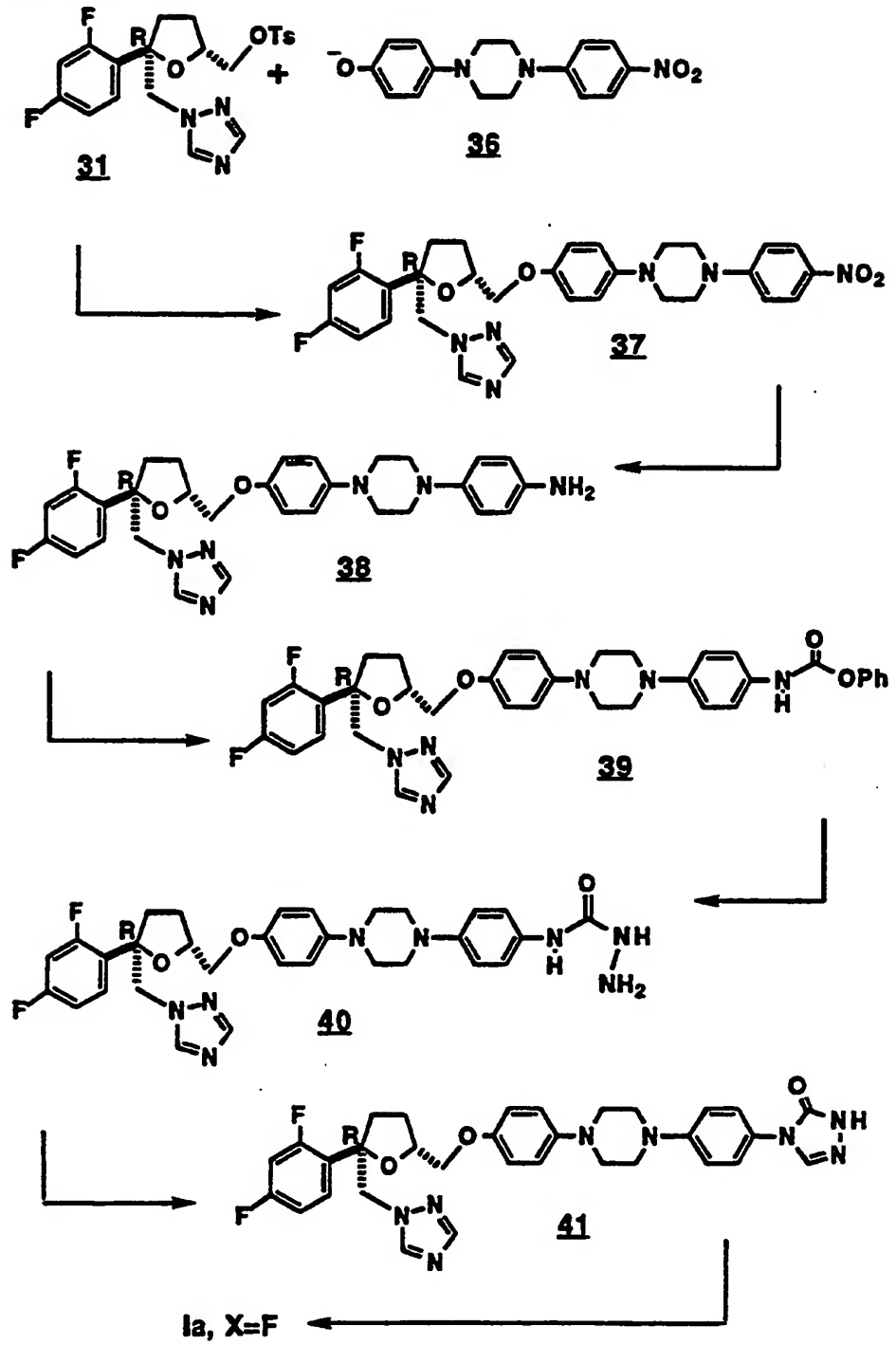
As can be seen from the above formulas and from other formulas in the specification, S or R is sometimes used to indicate the stereochemistry of a particular chiral center of a molecule.

SCHEME 5



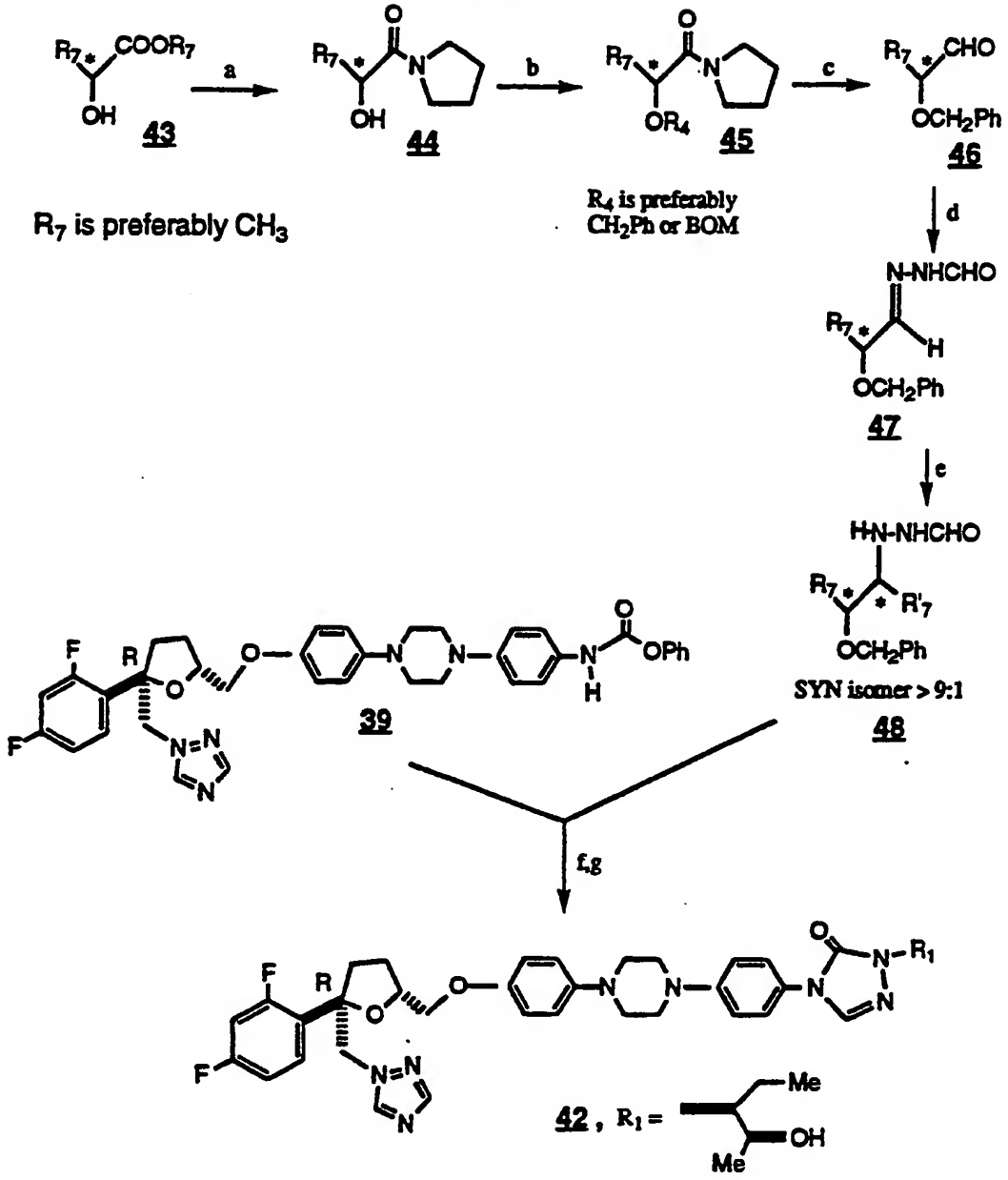
The reactions shown in the scheme 5 just above can be carried out in a manner analogous to that set forth in scheme 4, page 27 of commonly assigned copending U.S. Ser. No. 08/460,572, filed June 2, 1995. As used herein, SEM means $CH_2OCH_2CH_2SiMe_3$.

SCHEME 6



The reactions shown in the scheme 6 just above can be carried out in a manner analogous to that set forth in scheme V, page 28 of commonly assigned copending U.S. Ser. No. 08/460,572, filed June 2, 1995.

Scheme 7

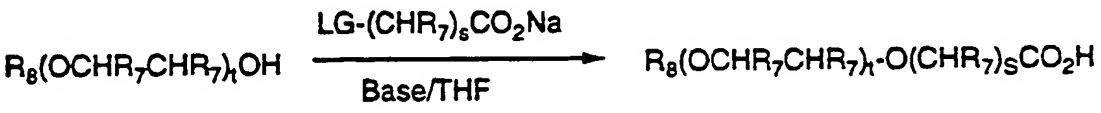


(a) pyrrolidine, r.t., 24 h; (b) R_7-X, NaH, DMF; (c) RED-AL, toluene. -20°; (d) $H_2NNHCHO$, MeOH; (e) R'_7MgBr, Et_2O, -10°C to r.t., 24 h; (f) toluene, DBU, 80°C, 6 Hours; 100°C, 16 hours; (g) H_2, Pd, HCOOH, 80°C.

wherein R_4 is CH_2Ph, CH_2CH_3 (MOM), $CH_2OCH_2CH_2OCH_3$ (MEM), $CH_2OCH_2CH_2SiMe_3$ (SEM), or CH_2OCH_2Ph (BOM).

The reactions shown in the scheme 7 just above can be carried out in a manner analogous to that set forth in scheme VI, page 29 of commonly assigned copending U.S. Ser. No. 08/460,572, filed June 2, 1995. LG is a leaving group such as chlorine.

Scheme 8



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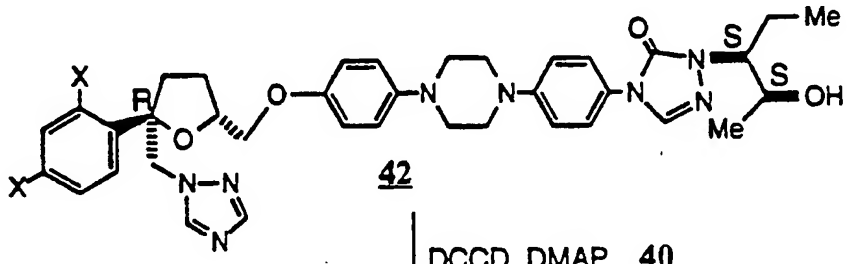

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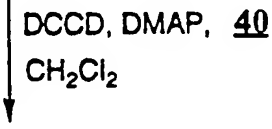

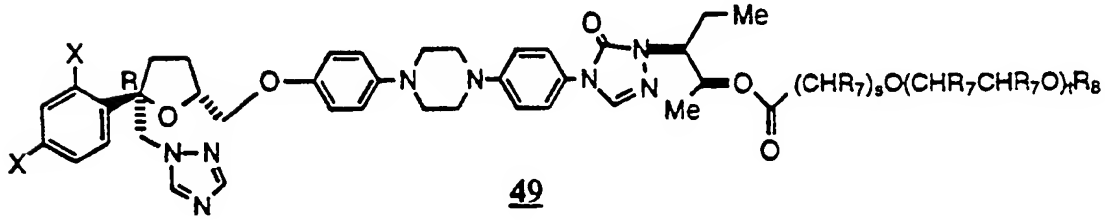

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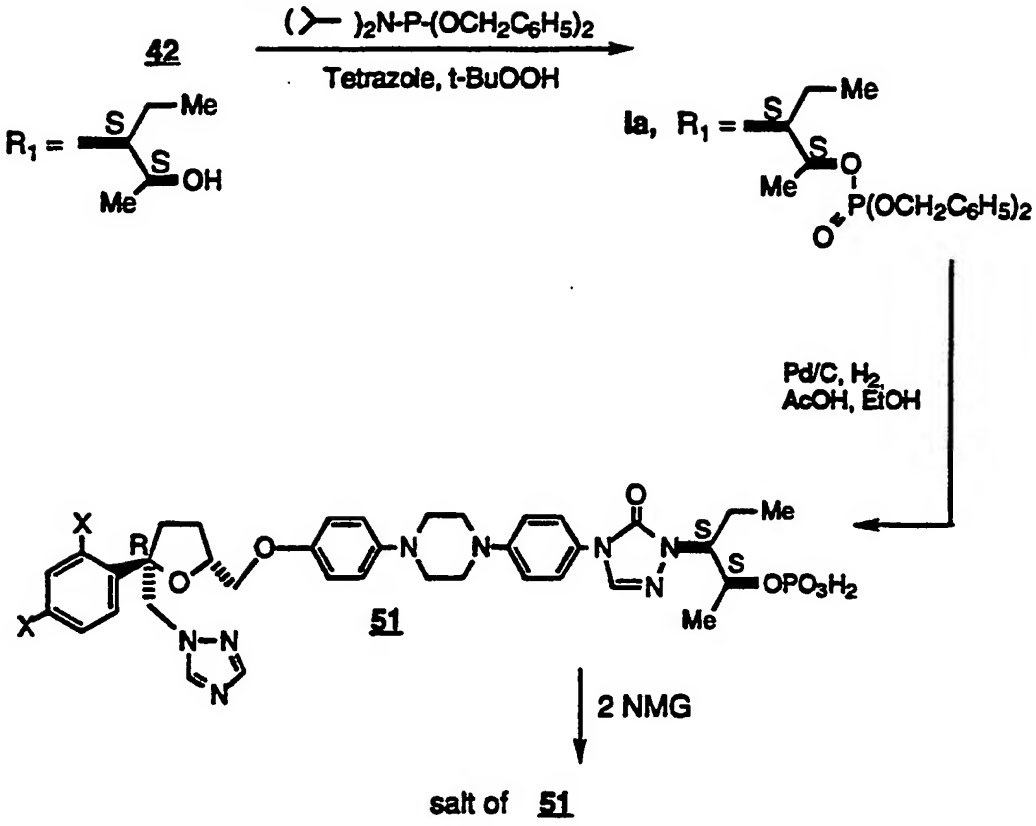
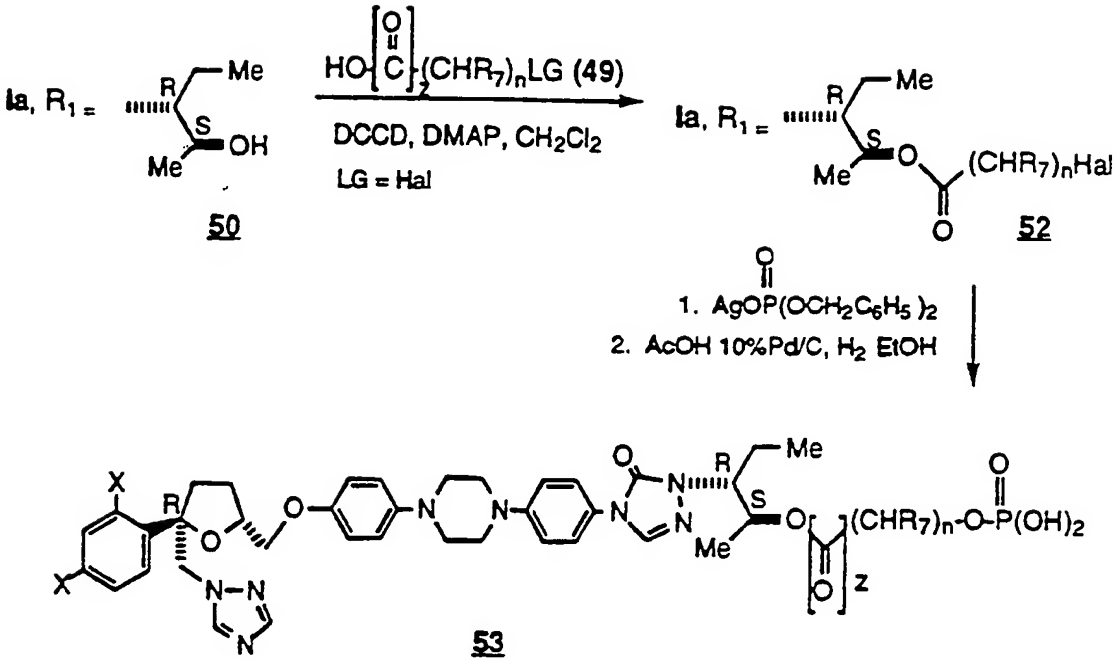
The reactions shown in the scheme 8 just above can be carried out in a manner analogous to that set forth in scheme VII, page 30 of commonly assigned copending U.S. Ser. No. 08/460,572, filed June 2, 1995.

Scheme 8a



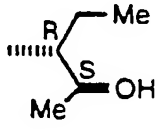
The reactions shown in the scheme 8a just above can be carried out in a manner analogous to that set forth in scheme VIIIA, page 31 of commonly assigned copending U.S. Ser. No. 08/460,572, filed June 2, 1995.

Scheme 9

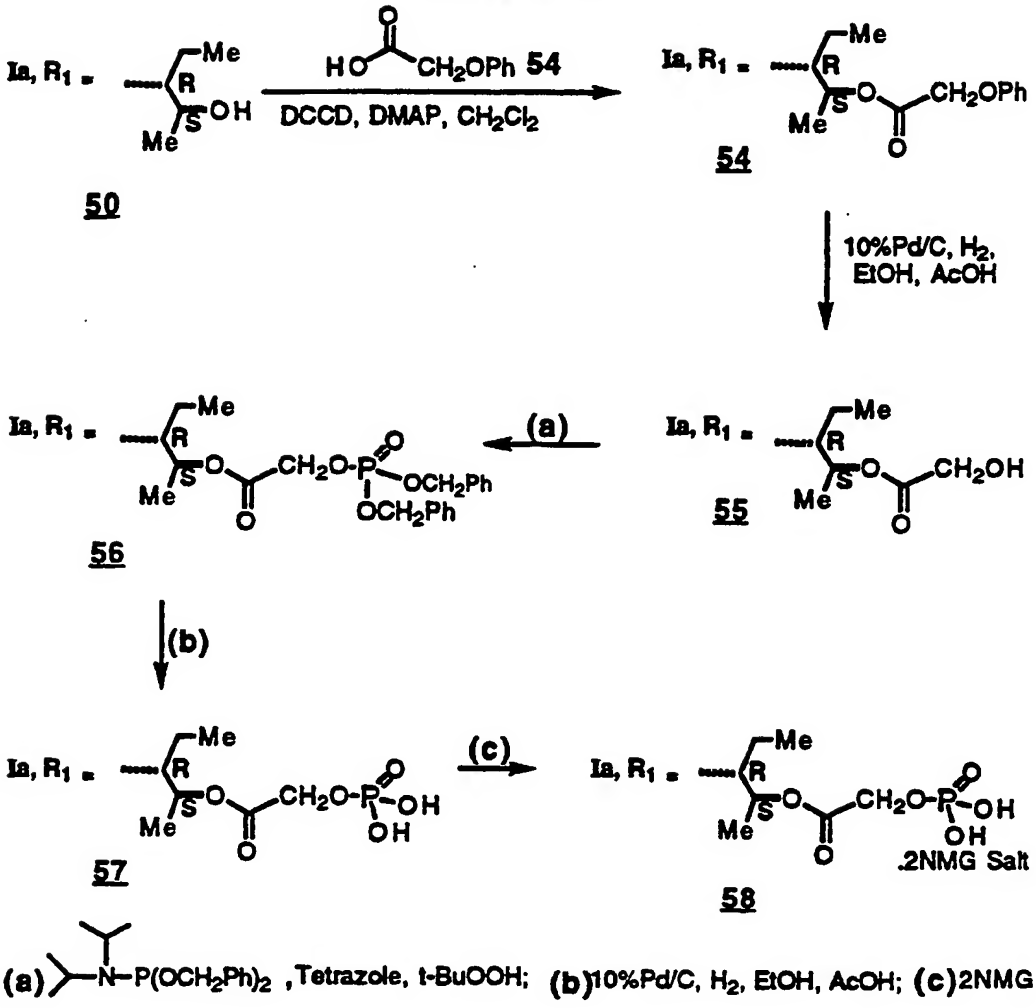


Hal=Br or Cl.

The reactions shown in scheme 9, above can be carried out in a manner analogous to that set forth in VIIIB , page 32 of commonly assigned copending U.S. Ser. No. 08/460,572, filed June 2, 1995.

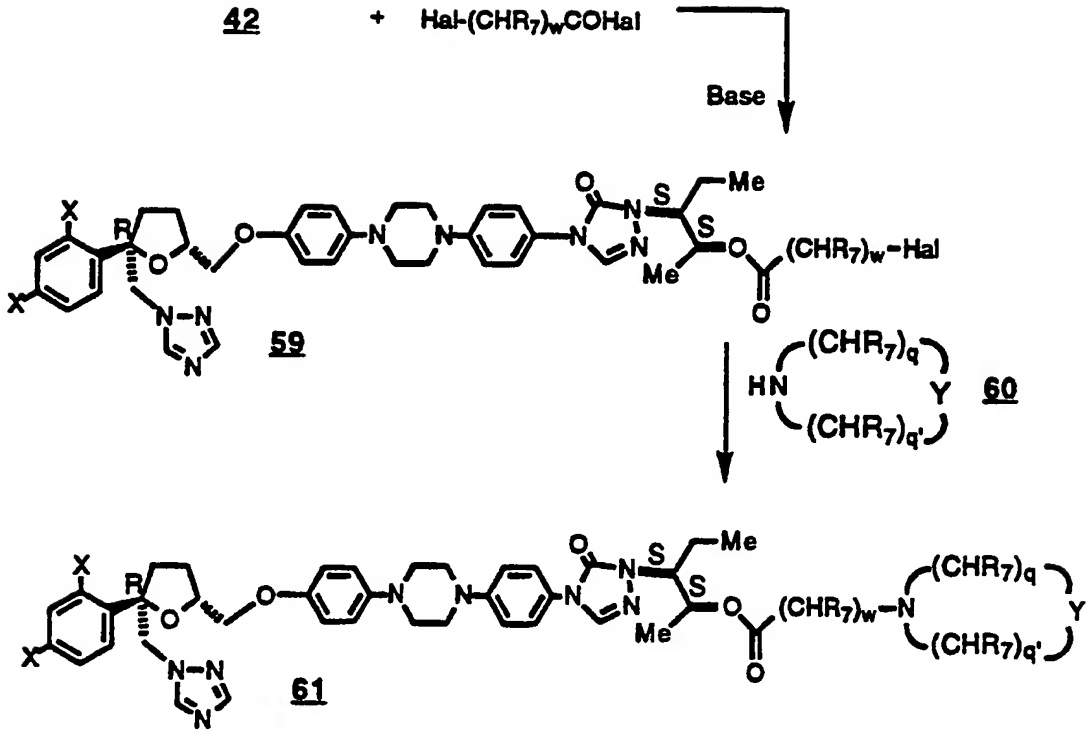
In the table just above, the compound Ia, when R_1 is  , is also referred to as compound 50. Similarly, two labels are also used for compound 52

Scheme 10



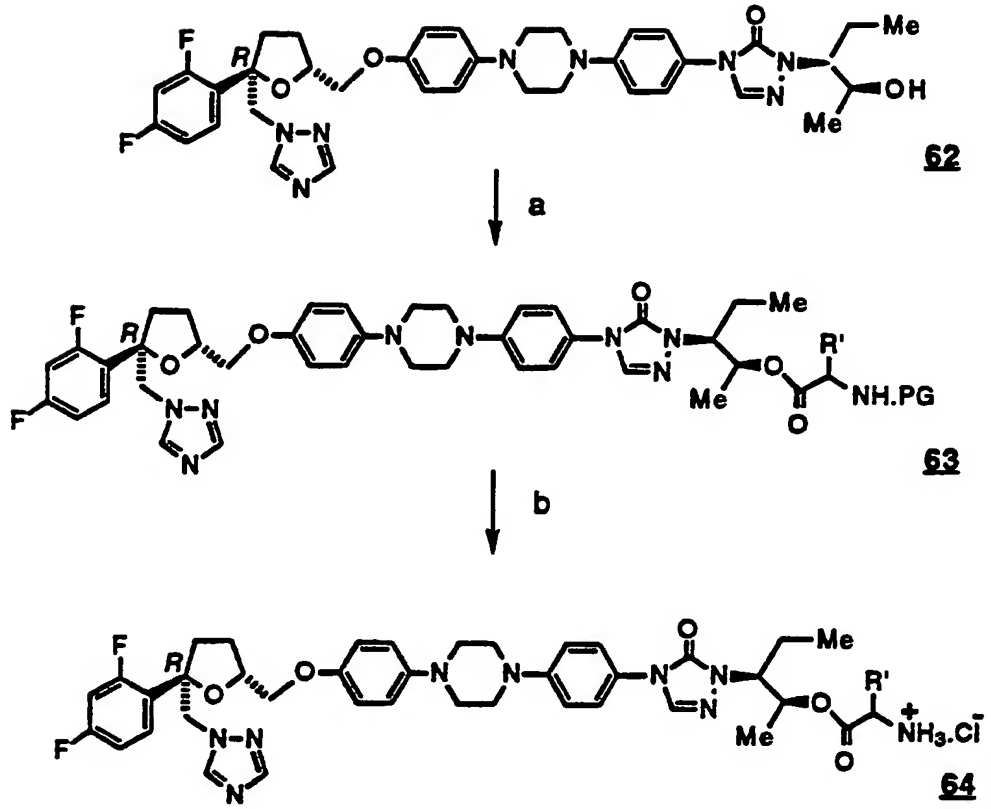
The reactions shown in scheme 10 just above can be carried out in a manner analogous to that set forth in scheme VIIIC, of page 34 of commonly assigned copending U.S. Ser. No. 08/460,572, filed June 2, 1995.

Scheme 11



The reactions shown in the scheme 11, just above can be carried out in a manner analogous to that set forth in scheme IX, page 36 of commonly assigned copending U.S. Ser. No. 08/460,572, filed June 2, 1995.

Scheme 12



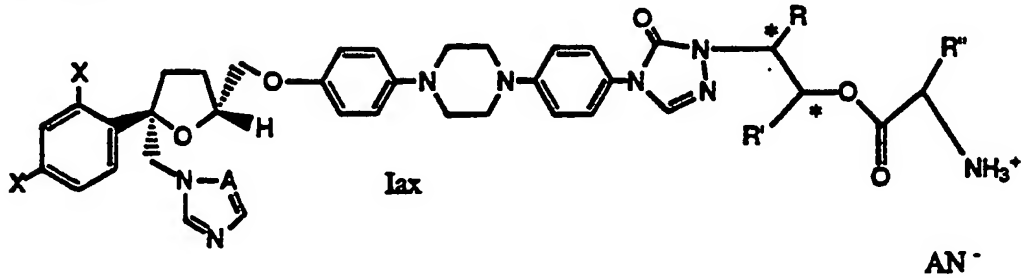
Reagents: (a) R'(NH.PG)CHCOOH, DCCD, DMAP, CH_2Cl_2; (b) HCl in dioxane

Where R' = H, CH_3, CH_2OH, $CH(OH)CH_3$, CH_2SH, CH_2CONH_2, $CH_2CH_2CONH_2$, $CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2CH_2SMe, CH_2COO^-, $CH_2CH_2COO^-$, $(CH_2)_4\overset{+}{N}H_3$, H_2C-(phenyl), H_2C-(phenyl)-OR_3, H_2C-(indole), H_2C-(imidazole), $H_2CH_2CH_2CH_2C$-(guanidinium); R_3= H, Phosphate ester, Sulphate ester, PG=CH_2Ph

The reactions shown in the scheme 12, just above can be carried out in a manner analogous to that set forth in scheme X, page 37 of commonly assigned copending U.S. Ser. No. 08/460,572, filed June 2, 1995.

Using an appropriate amino acid and an appropriate compound in place of compound 62, the reaction scheme 12, shown just above, can be carried out

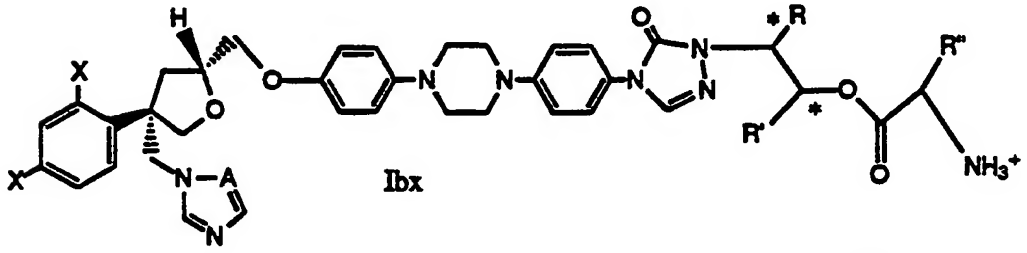
by one skilled in the art so as to arrive at any amino acid ester salts of the formulas



Iax

AN⁻

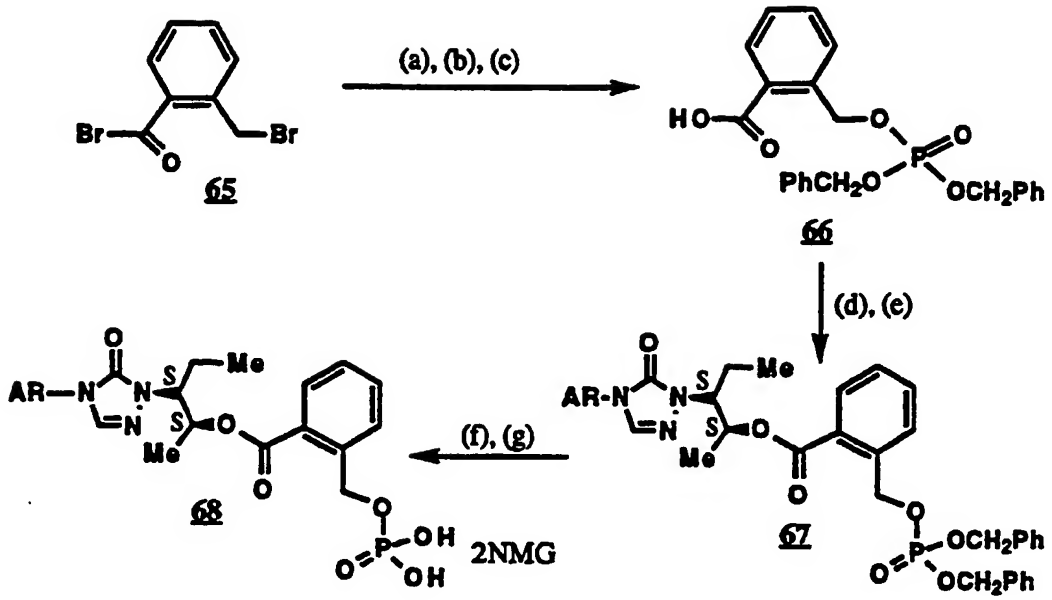
and



Ibx

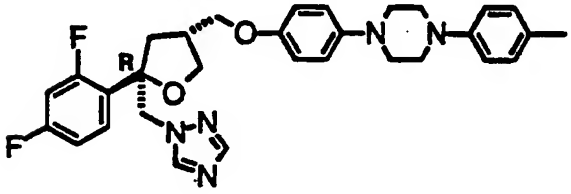
AN⁻

Scheme 13



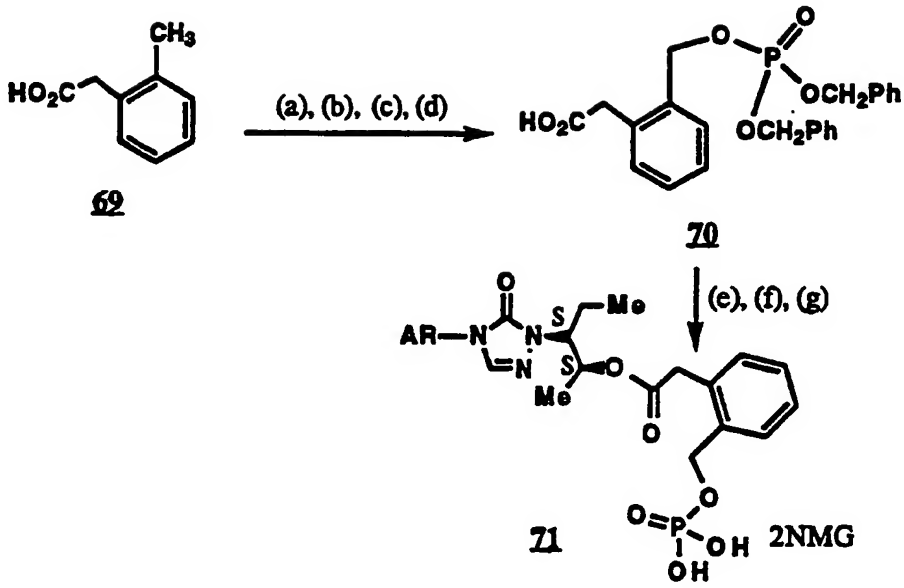
Reagents: (a) 2,2,2-trichloroethanol; (b) silver dibenzyl phosphate; (c) Zn, HOAc-THF; (d) $SOCl_2$; (e) 42; (f) H_2, 10% Pd-C; (g) 2eq. N- methyl glucamine.

As used in the Schemes 13 and 14 AR is



The reactions shown in the scheme 13, just above can be carried out in a manner analogous to that set forth in scheme XIA, page 38 of commonly assigned copending U.S. Ser. No. 08/460,572, filed June 2, 1995.

Scheme 14



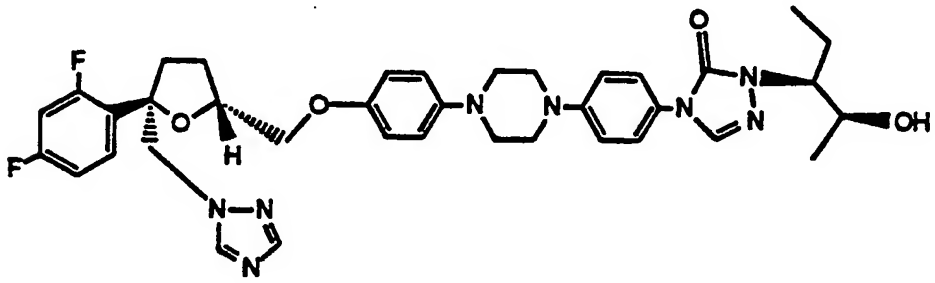
Reagents: (a) 2,2,2-trichloroethanol, DCCD, DMAP;(b) N-bromosuccinimide; (c) silver dibenzyl phosphate; (d) Zn, HOAc-THF; (e) compound 42 DCCD, DMAP; (f), H_2, 10% Pd-C; (g) 2eq. N- methyl glucamine

The reactions shown in the scheme 14, just above can be carried out in a manner analogous to that set forth in scheme XIB, page 39 of commonly assigned copending U.S. Ser. No. 08/460,572, filed June 2, 1995.

The compounds of this invention are prepared in accordance with Schemes hereinabove and the following Examples using commercially available starting materials, or using starting materials which can be prepared by known methods.

EXAMPLE OF THE PREPARATION OF [(R)-CIS]-4-[4-[4-[4-[[5-(2,4-DIFLUOROPHENYL)-TETRAHYDRO-5-[(1H-1,2,4-TRIAZOL-1-YL)METHYL]-2-

FURANYL]METHOXY]PHENYL]-1-PIPERAZINYL]PHENYL]-2-(1(S)-ETHYL-2(S)-HYDROXYPROPYL)-2,4-DIHYDRO-3H-1,2,4-TRIAZOL-3-ONE (42) which has the structural formula



COMPOUND 16, X=F

Add copper(I) iodide (50 mg) to a solution of 15, X=F (16 g) in anhydrous THF (300 mL). Stir the mixture and cool it to -70°C, and then slowly add a solution of 2.0 M allylmagnesium chloride in THF (52 mL). Allow the mixture to warm to r.t. and stir for an additional 3 hr. Quench the reaction with 1:1 saturated brine-10% aq. KH_2PO_4, extract with EtOAc, dry the extract over anhydrous Na_2SO_4, and filter the mixture. Evaporate the solvent and chromatograph the residue on silica gel with acetone-hexane to obtain the title compound 16, X=F (9.7 g), M^+ 280.3.

COMPOUND 17, X=F

A solution of the above olefin 16, X=F (11.2 g) in CH_2Cl_2 (250 mL) at -10°C is slowly treated with 85% purity *m*-chloroperbenzoic acid (9.0 g), and the mixture is then stirred at r.t. for 24 hr. The reaction mixture is washed with cold 5% aq. NaOH, then water, then saturated brine. The solution is dried over anhydrous $MgSO_4$, filtered, and the filtrate evaporated to leave the title compound 17,X=F (11.8 g), which is used without further purification.

COMPOUND 18, X=F

Stir and heat at 80°C a solution of the epoxide **17, X=F** from above (10 g), toluene (125 mL), and Et_3N (6.0 mL) for 2 hr. Suction-filter the hot mixture through a pad of silica gel and wash the pad with EtOAc. Evaporate the combined organics to leave a residue of a mixture of *cis*- and *trans*- alcohols. The residue is chromatographed on silica gel with MeOH-CH_2Cl_2 to give the title *cis*-compound **18, X=F** as the first of the isomers to elute.

COMPOUND **31** (**19, X=F**)

Stir a solution of the alcohol from above (12.4 g), Et_3N (5.9 mL), and DMAP (0.5 g) in CH_2Cl_2 (200 mL). Add tosyl chloride (8.2 g) and stir for 4 hours. Wash the mixture with cold aqueous 5% KH_2PO_4, and dry the organic layer over anhydrous Na_2SO_4. Filter the mixture, evaporate the filtrate to a residue, and crystallize the residue from EtOAc-$(i\text{-}Pr)_2O$ to obtain the tosylate **31** (4.2 g), mp 150-151°C.

COMPOUND **32**

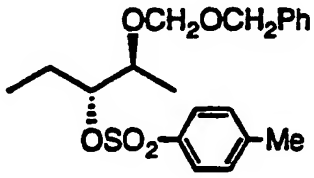
Stir a mixture of compound **30** (1.5 g), scheme 5, and Cs_2CO_3 (1.25 g) in DMF (50 mL) for 0.75 hours. Add the tosylate **31** from above (1.4 g) and stir at 80°C for 18 hours. Pour the mixture into aqueous 5% KH_2PO_4 and extract with EtOAc. Evaporate the extract and chromatograph the residue on silica gel to obtain compound **32** (1.4 g).

COMPOUND **33**

Stir a mixture of the compound **32** from above (1.4 g) in 1,4-dioxane (8 mL) and 12N HCl (15mL) at 90°C for 18 hours. Pour the mixture in water, add $NaHCO_3$ until the pH=4, and extract with EtOAc. Evaporate the extract and boil the residue in CH_3CN. Allow to cool and filter to leave compound **33** (0.7 g), FAB mass spectrum: M^+ 615.

COMPOUND 34, R_1 = (S,S)-CH(CH_3CH_2)[(CH(OCH_2OCH_2Ph)CH_3]

Stir a mixture of compound 33 (0.7 g) and Cs_2CO_3 (0.4 g) in DMF (20 mL) for 0.75 hours.



80

Add compound 80 (0.8 g), a compound which can be prepared by known means and stir at 80°C for 18 hours. Pour the mixture into aqueous 5% KH_2PO_4 , extract with EtOAc, evaporate the extract, and chromatograph the residue on silica gel to obtain compound 34 wherein R_1 = (S,S)-CH(CH_3CH_2)[(CH(OCH_2OCH_2Ph)CH_3] (0.5 g), FAB mass spectrum: M^+ 821.

COMPOUND 42

Stir a solution of the compound from above (0.5 g) in 1:1 MeOH-6N HCl (20 mL) for 5 hours. Add $NaHCO_3$ until the pH>4. Extract with EtOAc, evaporate the extract, boil the residue in Et_2O, and filter to leave compound 42 (0.35 g), mp 165-167°C; $[\alpha]_D$ +5.5° (c=0.5, CH_2Cl_2).

The mass spectral data presented herein as M^+ are parent ions which were determined by Fast Atom Bombardment (FAB) technique and represent the [$M+H^+$], i.e. {molecular ion+1} peaks.

Schemes 1-7 set forth the preferred processes to prepare the alcohol compounds of this invention.

As used in scheme 8 and elsewhere in this specification, the base 4-(N,N-dimethylamino)pyridine is referred to as "DMAP" and dicyclohexylcarbodiimide is referred to as DCCD.

The alkanoate and alkenoate esters of compounds of formula Ia and Ib are conveniently prepared by standard synthetic techniques, for example, by reaction of the anhydride or acid halide of the alkanoic acid or alkenoic acid in the presence of base e.g, pyridine.

The carbonic and carbamic esters of formulas 1a and 1b are conveniently prepared by standard synthetic techniques, for example, by the reaction of phosgene in the presence of a controlled amount of base, for example, pyridine, followed by reaction with an alcohol or amine in the presence of a base, for example, Et_3N and DMAP.

The sulfate esters may be prepared by reaction of the alcohol compounds of formulas I to IV with sulfur trioxide in the presence of excess pryridine at temperatures of 70°–90°C for at least 2 hours in accordance with the procedure of R.M. Moriarty et. al. Tetrahedron Letters, Vol. 35, No. 44, p 8103-8106 (1994).

Compounds represented by formula I exhibit broad spectrum antifungal activity, in conventional antifungal screening tests, against human and animal pathogens, such as the following: *Aspergillus, Blastomyces, Candida, Cryptococcus, Coccidioides, Epidermophyton, Fonsecaea, Fusarium, Mucor, Saccharomyces, Torulopsis, Trichophyton , Trichosporon, Sporothrix and Pneumocysitis.*

The antifungal compounds of formula I and pharmaceutical compositons of this invention are expected to exhibit anti-allergic, anti-inflammatory and immunomodulating activities, broad spectrum antiinfective activity, e.g., antibacterial, anti-protozoal and antihelminthic activities.

The present invention also provides a composition for treating or preventing fungal infections comprising an antifungally effective amount of a

compound represented by formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent therefor.

The pharmaceutical compositions of the present invention may also contain a fungicidally effective amount of other antifungal compounds such as cell wall active compound. The term "cell wall active compound", as used herein, means any compound that interferes with the fungal cell wall and includes, but is not limited to, compounds such as papulacandins, echinocandins, and aculeacins as well as fungal cell wall inhibitors such as nikkomycins, e.g, nikkomycin K and others which are described in USP 5,006,513 which is hereby incorporated by reference.

The pharmaceutically acceptable salts of the compounds of the present invention include pharmaceutically acceptable acid and base addition salts.

The preferred pharmaceutically acceptable acid addition salts are nontoxic acid addition salts formed by adding to the compounds of the present invention about a calculated amount of a mineral acid, such as HCl, HBr, H_2SO_4, HNO_3 or H_3PO_4, or of an organic acid, such as an alkyl or arylsulfonic acid such as maleic, lactic, methanesulfonic, isithionic, para- toluenesulfonic, naphthylsulfonic and the like.

The pharmaceutically acceptable bases found suitable for use in the present invention are those which form pharmaceutically acceptable salts of the acidic pharmaceutically acceptable esters of the antifungal compounds of formulas Ia and b , IIa and b , IIIa and b or IVa and b and include suitable organic and inorganic bases. Suitable organic bases include primary, secondary and tertiary alkyl amines, alkanolamines, aromatic amines, alkylaromatic amines and cyclic amines. Exemplary organic amines include the pharmaceutically acceptable bases selected form chloroprocaine, procaine, piperazine, glucamine, N-methylglucamine, N-N-dimethyl glucamine ethylendediamine, diethanolamine, diisopropylamine, diethylamine, N-

benzylenediamine, diethanolamine, diisopropylamine, diethylamine, N-benzyl-2-phenylethylamine, N-n'dibenzylethylenediamine, choline, triethylamine ("ET_3N"), tris(hydroxymethyl)aminomethane, or D-glucosamine. The preferred organic bases include N-methyl glucamine ("NMG"), diethanolamine, and tris(hydroxymethyl) aminomethane ("TRIS"). Use of two equivalents of NMG in this invention is more preferred. The suitable inorganic bases also include alkali metal hydroxides such as sodium hydroxide.

The pharmaceutical compositions of the present invention may be adapted for any mode of administration e.g., for oral, parenteral, e.g., SC, IM. IV and IP, topical or vaginal administration or by inhalation (orally or intranasally) Such compositions are formulated by combining the compound of formula Ia or Ib or an equivalent amount of a pharmaceutically acceptable salt of compound Ia or Ib with an suitable, inert, pharmaceutically acceptable carrier or diluent.

Examples of suitable compositions include solid or liquid compositions for oral administration such as tablets, capsules, pills, powders, granules, solutions, suppositories, troches, lozenges, suspensions or emulsions. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active compound. In the tablet, the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

Topical dosage forms may be prepared according to procedures well known in the art, and may contain a variety of ingredients, excipients and additives. The formulations for topical use include ointments, creams, lotions, powders, aerosols, pessaries and sprays.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredients

are dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. Liquid form preparations include, for example, water or water-propylene glycol solutions for parenteral injection. Liquid preparations can also be formulated in solution with an appropriate amount of a hydroxypropyl α- β or -γ-cyclodextrin having 2 to 11 hydroxypropyl groups per molecule of cyclodextrin, polyethylene glycol, e.g., PEG-200 or propylene glycol, which solutions may also contain water. Aqueous solutions suitable for oral use can be prepared by adding the active component in water and adding suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the active component in finely divided form in water. A particularly preferred aqueous pharmaceutical composition may be prepared from the compounds of formulas I to IV together with hydroxypropyl-β-cyclodextrin in water. The use of derivatives of α-, β- and γ-cyclodextrins, for example, hydroxpropyl-β-cyclodextrin are disclosed by N. Bodor USP 4,983,586, Pitha USP 4,727,064 and Janssen Pharmaceutical International Patent Application No. PCT/EP 84/00417.

The pharmaceutical compositions of the present invention may be prepared by admixing the pharmaceutically acceptable carrier, e.g., a hydroxypropyl-β-cyclodextrin in water, and adding thereto an antifungally effective amount of a drug of the present invention. The solution so formed is filtered, and optionally, the water may be removed by well known methods, e.g., rotatory evaporation or lyophilization. The formation of the solution may take place at a temperature of about 15° to 35°C. The water is normally sterilized water and may also contain pharmaceutically acceptable salts and buffers, e.g., phosphate or citrate as well as preservatives. The molar ratio of the antifungal

compound of formula I to hydroxpropyl-β-cyclodextrin is about 1:1 to 1:80, preferably 1:1 to 1:2. Normally the hydroxypropyl-β-cyclodextrin is present in molar excess.

Also included are solid form preparations which are intended to be converted, shortly before use, into liquid form preparations for either oral or parenteral administration. The solid form preparations intended to be converted to liquid form may contain, in addition, to the active materials, such as compounds of this invention, and optionally a cell wall active compound, especially a fungal cell wall inhibitor, e.g., a nikkomycin, flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents and the like. The solvent utilized for preparing the liquid form preparations may be water, isotonic water, ethanol, glycerin, polyethylene glycols, propylene glycol, and the like, as well as mixtures thereof.

Parenteral forms to be injected intravenously, intramuscularly, or subcutaneously are usually in the form of a sterile solution, and may contain salts or glucose to make the solution isotonic.

The topical dosage for humans for antifungal use in the form of a pharmaceutical formulation comprising a compound of formula I (usually in the concentration in the range from about 0.1% to about 20% preferably from about 0.5% to about 10% by weight) together with a non-toxic, pharmaceutically acceptable topical carrier, is applied daily to the affected skin until the condition has improved.

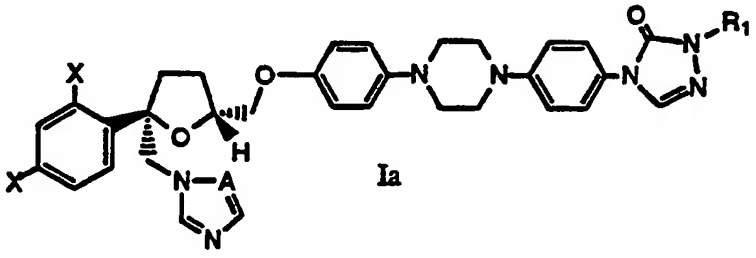
In general, the oral dosage for humans for antifungal use ranges from about 1 mg per kilogram of body weight to about 30 mg per kilogram of body weight per day, in single or divided doses, with about 1 mg per kilogram of body weight to about 20 mg per kilogram of body weight per day being preferred and the dose of about 1 mg per kilogram of body weight to about 10 mg per kilogram of body weight per day being most preferred.

In general, the parenteral dosage for humans for antifungal use ranges from about 0.25 mg per kilogram of body weight per day to about 20 mg kilogram of body weight per day, in single or divided doses, with about 0.5 to about 10 mg per kilogram of body weight per day being preferred.

The exact amount, frequency and period of administration of the compounds of the present invention for antifungal use will vary, of course, depending upon the sex, age and medical condition of the patent as well as the severity of the infection as determined by the attending clinician.

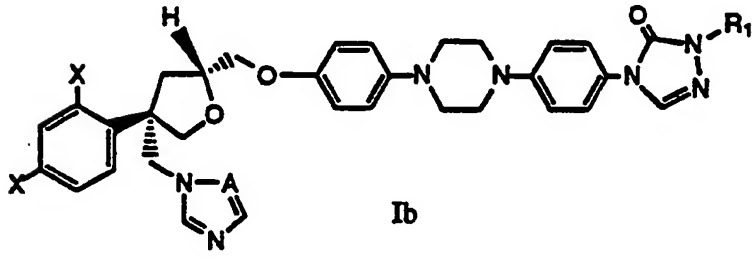
What is Claimed is:

1. A compound represented by a formula selected from the group consisting of



Ia

and



Ib

wherein X is independently selected from the group consisting of F, Cl, Br, and CF_3;

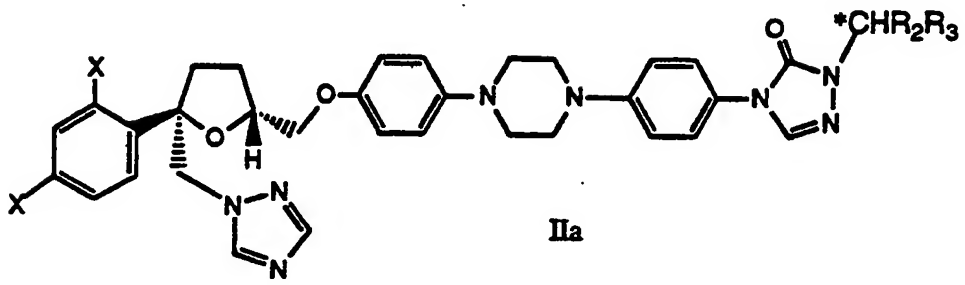
R_1 is a straight or branched chain (C_3 to C_8) alkyl group substituted by one or two hydroxy moieties, and esters thereof;

A is N or CH;

or a pharmaceutically acceptable salt thereof.

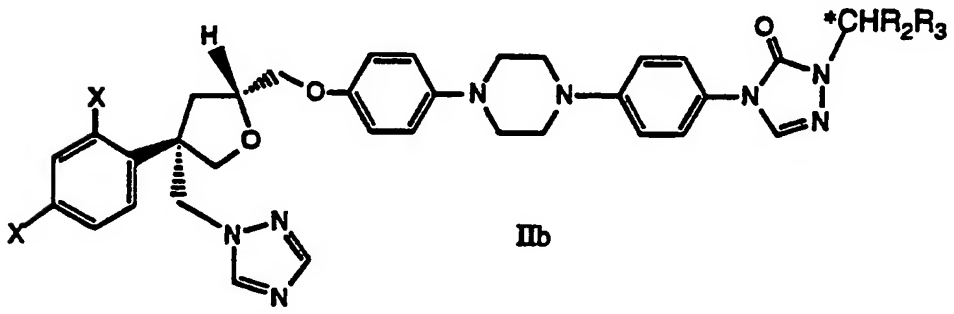
2. A compound of claim 1 wherein R_1 is a straight or branched chain (C_4-C_5) alkyl group substituted by at least one hydroxy moiety.

3. A compound of claim 1 represented by a formula selected from the group consisting of



IIa

and



IIb

wherein X is independently selected from the group consisting of F, Cl Br, and CF_3;

wherein R_2 is H or (C_1-C_3) alkyl and R_3 is (C_1-C_3) alkyl substituted by one hydroxy moiety and the carbon with the asterisk (*) has the R or S absolute configuration;

an ester thereof or a pharmaceutically acceptable salt thereof.

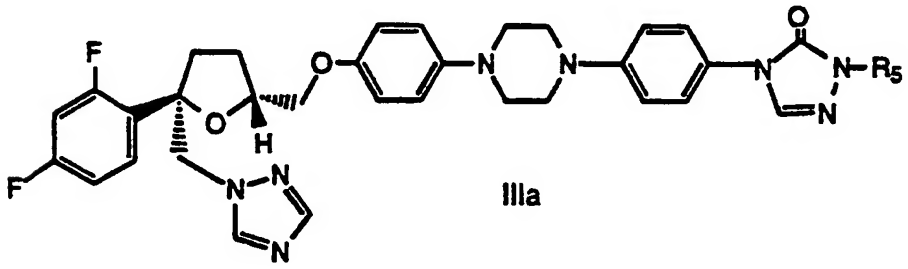
4. A compound of claim 3 wherein R_2 or R_3 is (C_1-C_2)alkyl and each X is F.

5. A compound of claim 1 wherein R_1 is a hydroxy-substituted C_4- or C_5-alkyl group selected from:

$-\overset{*}{C}H(C_2H_5)\overset{*}{C}H(R_4)CH_3$, $-\overset{*}{C}H(C_2H_5)CH_2CH_2R_4$,
$-(CH_2)_2\overset{*}{C}H(R_4)C_2H_5$, $-\overset{*}{C}H(CH_3)\overset{*}{C}H(R_4)CH_3$,
$-\overset{*}{C}H(C_2H_5)CH_2R_4$ and $-\overset{*}{C}H(CH_3)CH_2CH_2R_4$

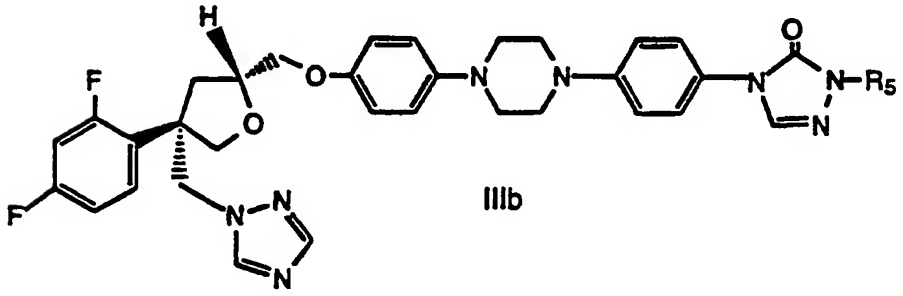
wherein R_4 is OH or an ester thereof and the carbons with the asterisk(*) have the R or S absolute configuration or a pharmaceutically acceptable salt thereof.

6. A compound of claim 1 represented by a formula selected from the group consisting of



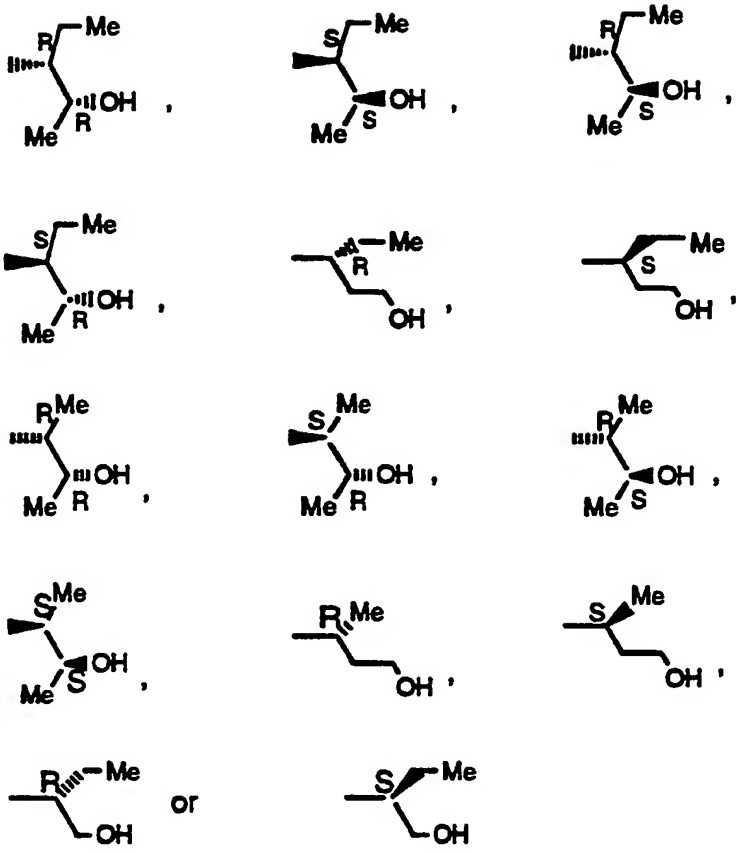
IIIa

and



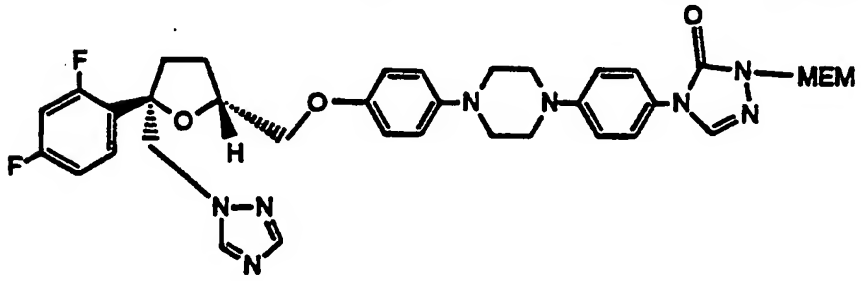
IIIb

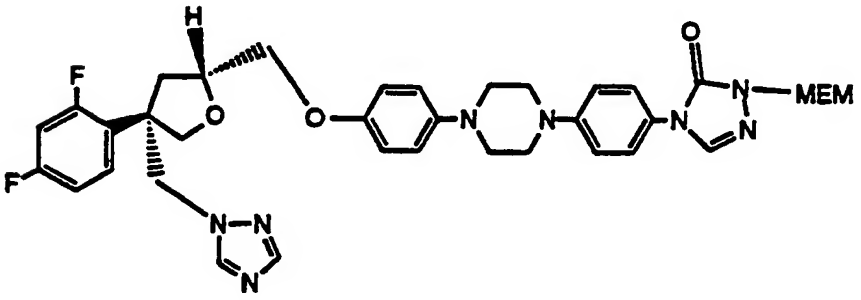
wherein R_5 is



or an ester thereof or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 1 selected from the group consisting of





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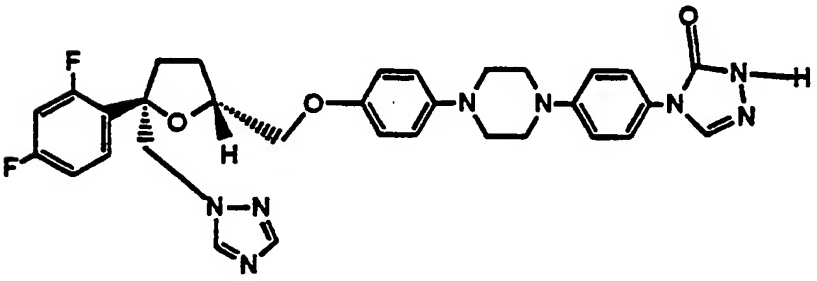

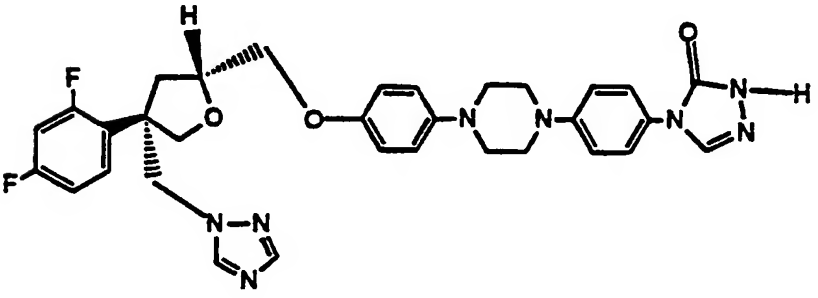

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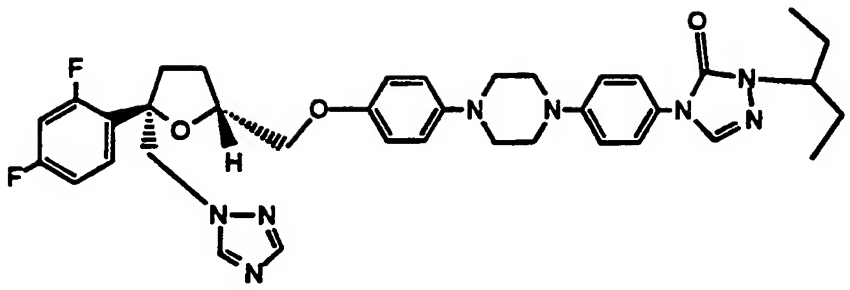

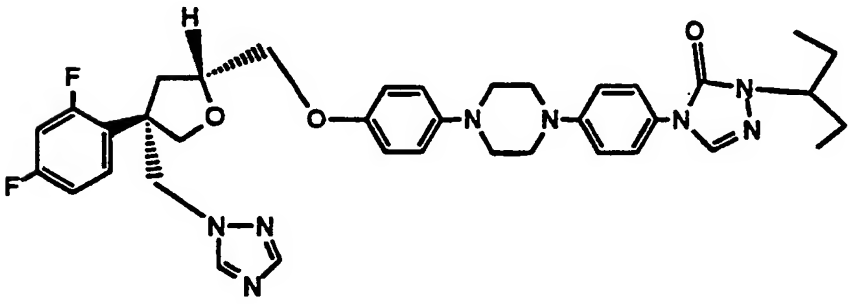

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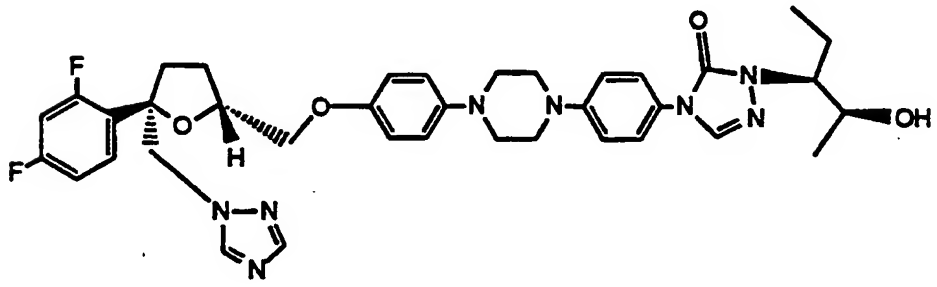

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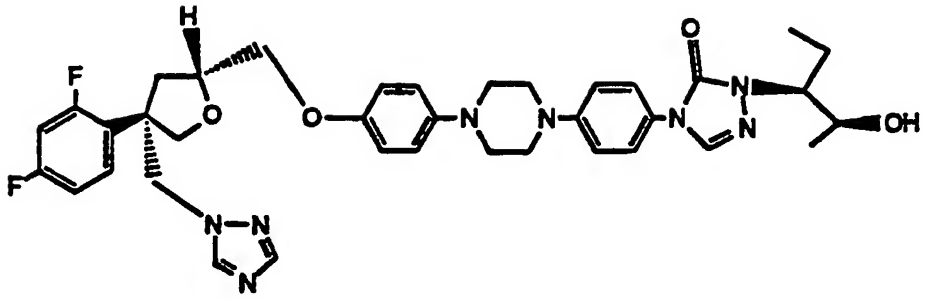
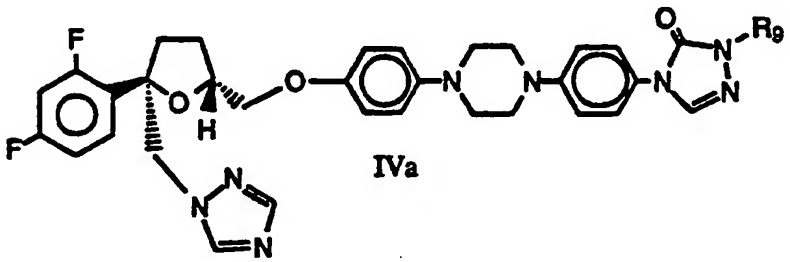
and



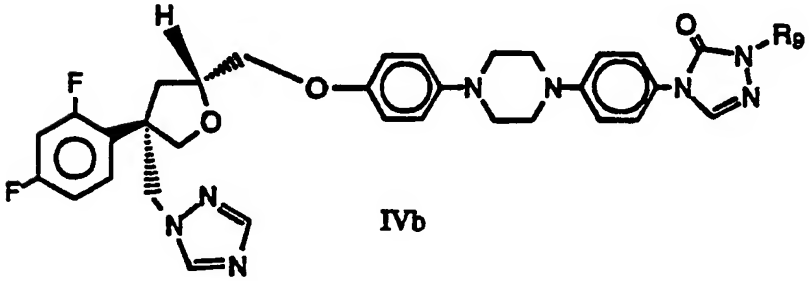
or a pharmaceutically acceptable salt thereof.

8. A compound of claim 1 represented by a formula selected from the group consisting of



IVa

and

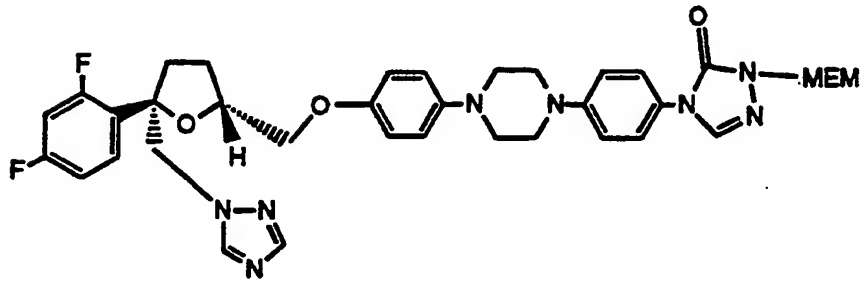


IVb

wherein R_9 = $-\overset{*}{C}H(C_2H_5)CH(R_6)CH_3$ or $-\overset{*}{C}H(CH_3)CH(R_6)CH_3$

wherein R_6 is OH, or an ester thereof or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 1 selected from the group consisting of



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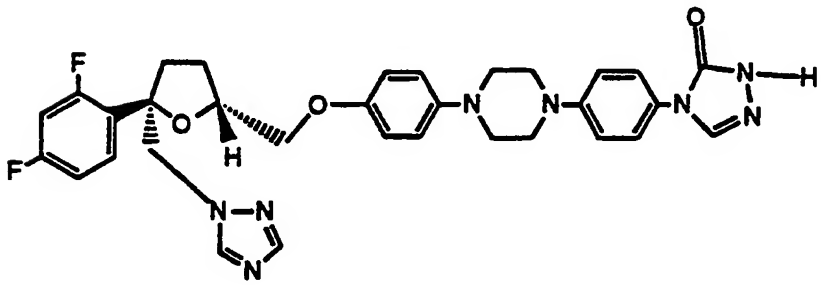

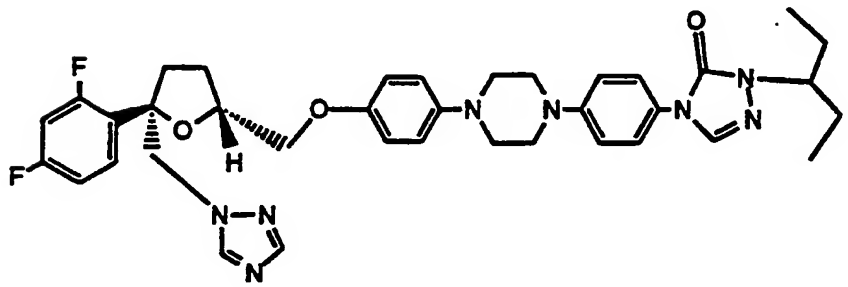

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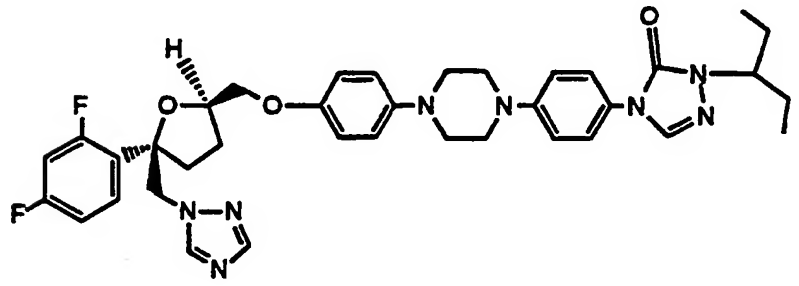
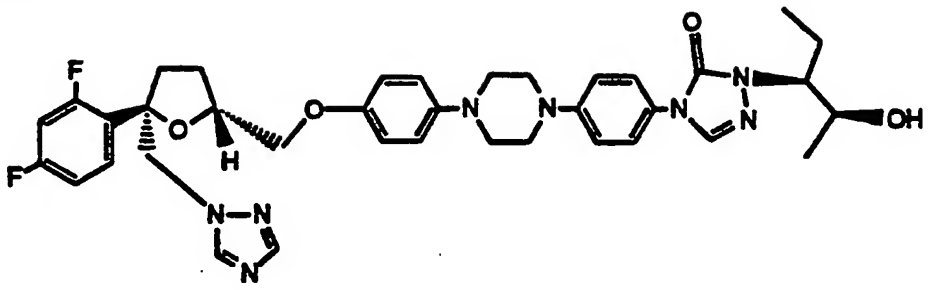
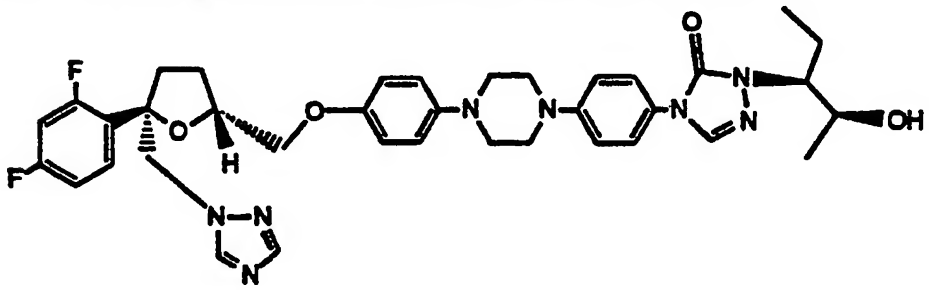


and



or a pharmaceutically acceptable salt thereof.

10. The compound according to claim 1 of the formula



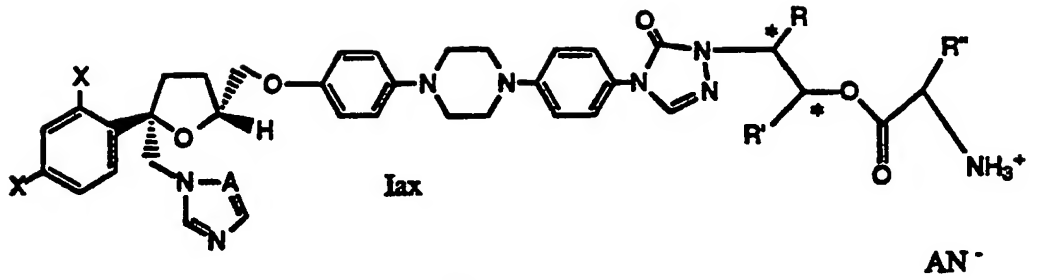
or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition for treating or preventing fungal infection comprising an antifungally effective amount of a compound of claim 1 together with a pharmaceutically acceptable carrier therefor.

12. A method of treating and/or preventing fungal infections in a mammal afflicted with same which comprises administering an antifungally effective amount of a compound of claim 1 sufficient for such treating or preventing.

13. The method of claim 12 wherein the mode of administration is oral or parenteral.

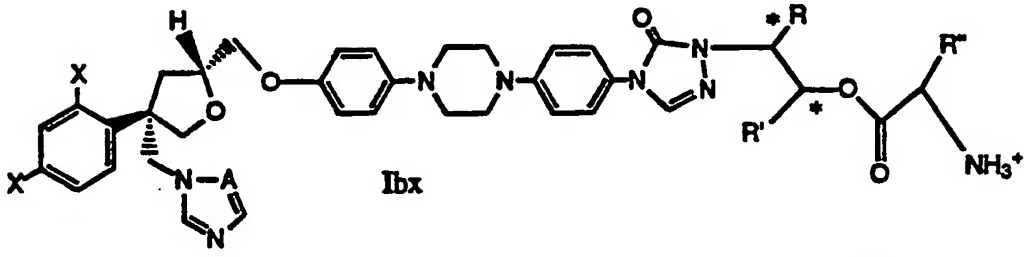
14. An amino acid ester salt represented by a formula selected from the group consisting of:



Iax

AN⁻

and



Ibx

AN⁻

wherein X is independently selected from the group consisting of F, Cl Br, and CF_3;

A is N or CH;

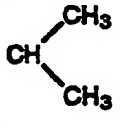
R is H, CH_3, or C_2H_5,

R' is H, CH_3, C_2H_5 ,

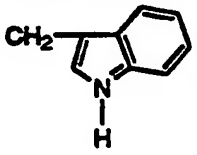
AN^- is an anion;

R" is H, CH_3, CH_2OR''', $CH(OR''')CH_3$; CH_2SR''',

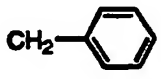
, CH_2CONH_2, $CH_2CH_2CONH_2$,



,



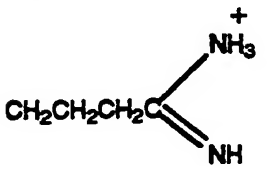
$CH(CH_3)CH_2CH_3$,



,

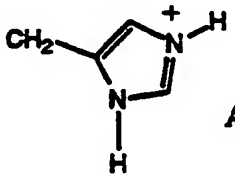
, $CH_2CH_2SCH_3$,

$CH_2COO^-M^+$, $CH_2CH_2COO^-M^+$, $CH_2CH_2CH_2CH_2NH_3^+AN^-$



AN-

,



AN^-

,

M^+ is a metal cation; and

R''' is H, phosphate ester, sulphate ester and proline ester.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 96/09242

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D405/14 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 539 938 (SCHERING CORPORATION) 5 May 1993 see pages 14,15,24,25 and claims	1-14
P,Y	WO,A,95 17407 (SCHERING CORPORATION) 29 June 1995 see claims	1-14
P,Y	WO,A,95 19983 (JANSSEN PHARMACEUTICA N.V.) 27 July 1995 see claims	1-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 September 1996	13.09.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US96/09242

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark : Although claims 12, 13 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/US 96/09242

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-539938	05-05-93	AU-B-	665218	21-12-95
		AU-B-	2916992	07-06-93
		CA-A-	2122270	13-05-93
		CN-A-	1073944	07-07-93
		CZ-A-	9401027	15-03-95
		EP-A-	0610377	17-08-94
		FI-A-	941986	29-04-94
		HR-A-	921145	11-08-94
		HU-A-	70742	30-10-95
		JP-T-	7500605	19-01-95
		NO-A-	941589	23-06-94
		NZ-A-	244910	26-01-96
		SK-A-	48894	08-02-95
		WO-A-	9309114	13-05-93
		ZA-A-	9208342	29-04-93
WO-A-9517407	29-06-95	AU-B-	1512795	10-07-95
		NO-A-	962616	07-08-96
WO-A-9519983	27-07-95	AU-B-	1535595	08-08-95
		NO-A-	963073	23-07-96